PROTOCOL TITLE

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE); A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenoses in haemodialysis access

Trial Identifiers ISRCTN – 14284759 REC Number – 15/LO/0638

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Study Synopsis

Title	**P**aclitaxel assisted balloon **A**ngioplasty of **V**enous stenosis in ha**E**modialysis access.
Protocol Short Title	PAVE Trial
Protocol Version number/ Date	Version 6.0 07/07/2016
Is the study a Pilot?	No
Study Hypothesis	The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.
Methodology	Double-blind multicentre randomised controlled trial
Sponsor name	King's College London / GSTT NHS Foundation Trust
Chief Investigator	Dr Michael Robson
REC number	15/LO/0638
Condition under investigation	Arteriovenous fistulae used for haemodialysis in patients with end stage kidney disease.
Purpose of clinical trial	RCT to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.
Number of Patients	211
Trial Design	Double-blind multicentre randomised controlled trial with variable follow up (minimum 1 year)
Endpoints	The primary endpoint is time to end of target lesion primary patency (TLPP). Secondary endpoints: 1. Angiographically determined late lumen loss 2. The rate of binary angiographic re-stenosis 3. Time to end of access circuit primary patency 4. Time to end of access circuit cumulative patency 5. Procedural success 6. Number of thrombosis events 7. Total number of interventions 8. Adverse events 9. Patient quality of life assessed by EQ-5D and POS-S Renal
Inclusion Criteria	1. Patients (18 years or over) who have a native AVF in the arm 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. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon 5. A residual stenosis of ≤ 30% after plain balloon fistuloplasty 6. A treatment segment, containing one or more lesions, which can be treated with ≤120 mm of a single drug-coated balloon
Exclusion Criteria	1. Patient unable to give informed consent 2. Patient unwilling or unable to comply with all study-related procedures 3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure. 4.One or more lesions outside the treatment segment, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit 5. Location of stenosis central to the thoracic inlet 6. Thrombosed (failed) access circuit at time of treatment 7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children within two years of study treatment 8. Known hypersensitivity or contraindication to contrast medium which cannot be

	adequately premedicated 9. Known hypersensitivity or contraindication to paclitaxel
Statistical Methodology and Analysis	To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis.

Device Name	Lutonix 035 Drug Coated Balloon PTA Catheter (Treatment) Ultraverse 035 PTA Dilatation Catheter (Placebo) Dorado PTA Dilatation Catheter (Plain balloon)
Manufacturer Name	C.R Bard, Inc.
Principle intended use	Angioplasty of stenosed blood vessels
Is the device CE-marked and used within its purpose?	Yes
Is the device currently used within the department?	Yes

Description and Maintenance and storage of device
The balloons will be stored under routine conditions in the radiology department.
No special measures or maintenance is needed.

Are the devices registered on the DoH MIA Master Indemnity Scheme?	Yes

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
Atm	Atmospheres (pressure)
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
ISRCTN	International Standard Randomised Controlled Trial Number
REC	Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
PTA	Percutaneous Transluminal Angioplasty
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
PCB	Paclitaxel-coated balloon
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSA	Site Specific Assessment

TLPP	Target Lesion primary patency
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

1.1. Existing research

Vascular access for haemodialysis

The 2012 UK Renal Registry report (www.renalreg.com) found that 43.9% of patients with end-stage kidney disease in the UK are on haemodialysis. This equated to 365 patients per million population in the UK in 2011. This number has increased every year with an overall increase of 3.6% from 2006 to 2011. In order to perform haemodialysis, reliable vascular access is essential. It is universally agreed that the optimal form of access is a native arteriovenous fistula (AVF) are superior to synthetic arteriovenous grafts (AVGs) and tunnelled central venous catheters for haemodialysis access, AVFs and AVGs have limited lifespans. Data from the Dialysis Outcomes and Practice Study (DOPPS) showed that in the US the one year patency for AVFs and AVGs is 68% and 49% respectively. In Europe, one-year AVF survival was somewhat better at 83% but there is still a need for improvement [1]..

Problems with vascular access are an important cause of morbidity and mortality in haemodialysis patients. In the US, it has been estimated that $1bn per year is spent on vascular access and its complications [2]. A recent survey in the UK found that haemodialysis patients occupy 320,000 bed days per year, with 30% of admissions related to vascular access (Renal Association vascular access audit, available at www.renal.org). When thrombosis or stenosis occurs in an AVF or AVG, a central venous catheter may be used for several months until an AVF or AVG is formed and becomes usable. Data from the US has shown that the risk of invasive infection is increased 100 fold in haemodialysis patients compared to the general population. 85% of those diagnosed with an infection have an invasive device in situ. 90% of those diagnosed with an infection require hospitalisation and there is a 17% associated mortality [3]. It is therefore imperative to preserve each AVF or AVG for as long as possible and to minimise the use of central venous catheters.

The initial therapy for a stenosis in an AVF is radiological fistuloplasty. A major concern however is the longevity of this effect. Turmel-Rodrigues et al reported the outcomes of interventional salvage of dysfunctional and thrombosed haemodialysis circuits [4]. There were 220 cases in the dysfunctional AVF group. The 6, 12, 24 month primary patency (AVF working with no repeat intervention) reported were 67%, 51% and 37% for forearm AVF and 57%, 35% and 24% for upper arm AVF respectively. Bountouris et al. reported the outcomes after 159 percutaneous transluminal angioplasties (PTAs) in AVFs. The primary patency at 6, 12 and 24 months were 61%, 42% and 35% respectively [5]. Primary assisted patency (AVF working regardless of repeat intervention) was 89% and 85% at 6 and 12 months respectively. Although there have been some exceptions [6, 7], most other studies have reported similar primary patency rates of around 40-50% at one year [8-10].

The biology of arteriovenous fistula dysfunction

In addition to the need for better interventions to reduce restenosis rates, there is also a need to better understand and identify the different types of response that occur following intervention. Neointimal hyperplasia leads to stenoses in the venous segments of AVFs, with the pathology characterised by an expansion of alpha smooth muscle actin positive myofibroblasts in the

neointima [11]. In arteries, the contribution of bone-marrow derived cells to tissue repair depends on the nature and severity of injury [12]. The contribution of bone marrow cells to venous neointimal hyperplasia is not resolved and the data from animal studies are conflicting. Two studies using bone marrow transplantation with cells containing a green fluorescent protein (GFP) or β-galactosidase reporter gene, have suggested a minimal contribution of bone-marrow derived cells in mouse and rat model respectively [13, 14]. However a further study employing a murine vein graft, has suggested that at least 20% of neointimal cells may be bone marrow derived [15]. GFP positive cells were detected by a more sensitive PCR method and these technical differences were suggested as a reason for discrepancies with other studies.

In addition to these conflicting data on the origin of neointimal cells, it should be noted that none of the previous reports induced vein injury in a way that mirrors the changes induced by angioplasty. Instead, most have focussed on the development of primary stenosis in venous conduits undergoing arterialisation where endothelium is 'traumatised' or activated by changes in the flow characteristics of arterial blood to which it becomes exposed. Given the data from arterial studies, a contribution from bone marrow cells to the alpha smooth muscle actin producing cells in the hyperplastic neointima of a dysfunctional AV fistula is highly likely with the degree of trauma to the endothelium that would follow angioplasty. Angioplasty causes vessel wall damage with rupture of the junction between the intima and the media, with a burst of proliferation and repair. Much of our understanding of aggressive neointimal formation in this context comes from arterial studies [16], but similar pathology and an increase in proliferation has been shown in AVFs following venous angioplasty [17].

Paclitaxel exerts an antiproliferative effect by interfering with cell microtubule function [18]. Systemic administration of paclitaxel after angioplasty in the rat carotid artery showed that a significant reduction in neointimal proliferation could be achieved at doses much lower than antineoplastic levels [19]. In rat and human cultured cell models, paclitaxel inhibited vascular smooth muscle cell migration and proliferation [19, 20], consistent with its effects in vivo. As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimising systemic toxic effects. Proof of this possibility was initially shown using paclitaxel-coated stents in pig coronary arteries [21].

Recent advances in technology have allowed angioplasty balloons to be coated with paclitaxel. This allows local delivery of paclitaxel to the site of stenosis. A number of multi-centre randomised controlled trials in the coronary and peripheral arterial circulation have established the positive benefit of drug-coated balloons (DCBs) [22, 23]. A small pilot study has suggested efficacy in dialysis patients [24, 25]. In this study, 40 patients with dysfunctional AVFs or AVGs were randomised to receive either DCB or Plain Balloon Angioplasty (PBA). Primary unassisted patency (defined angiographically as a binary readout of <50% stenosis) in the DCB group was significantly better than the PBA group at 6 (70% v 25%) and 12 months (35% v 5%, $p<0.001$) respectively. This study may be criticised on a number of points. These include the use of an angiographic rather than a clinical endpoint, the lack of blinding and independent angiographic core lab analysis and the very small sample size originally intended to test non-inferiority only (with a wide 15% non-inferiority limit). In addition, a range of balloons was used in the control group for post-dilation after the paclitaxel-coated balloons, and these were not universally high pressure and non-compliant. This may have added variability to the outcome. Furthermore, the inclusion of both AVFs (35%) and AVGs (65%) may have resulted in significant confounding, given the difference in survival rates associated to the two types of access. Despite these limitations, the results suggested that a further study of efficacy was warranted, which is what we propose here.

The PAVE trial is the first large scale randomised controlled trial designed to test superiority of DCBs in native haemodialysis access circuits. Further, the impact on patient quality of life will be performed.

1.2. 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 paclitaxel-coated balloon or control balloon following this initial dilatation. The paclitaxel-coated balloons that will be used are CE marked and there have been no safety concerns with their use. In the specific context of haemodialysis AVFs, the pilot study performed did not raise any safety concerns [24].

1.3. Rationale for current study:

The overriding aim of this study is preservation of vascular access for haemodialysis with a reduction in restenosis and the need for repeat fistuloplasties.

Clinical Trial

Our hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic AVFs. As detailed in section 1.1, this hypothesis is supported by what is known of the effects of paclitaxel on the biology of neointimal formation, results in trials involving coronary and peripheral arteries, and a pilot study vascular access for haemodialysis.

This need for repeat procedures following angioplasty is expensive and inconvenient for patients and is needed in around 60% of patients during the first year [5]. As detailed in our sample size calculation we predict that the use of paclitaxel coated balloons will lead to an avoidance of the need for repeat angioplasty. Repeat angioplasties will also have a negative effect on patient quality of life and a reduction in these will be a benefit in addition to the reduction in cost.

Collection of patient samples

Patient blood samples will also be collected within the setting of the clinical trial. This will form an important resource for future laboratory based studies on biomarkers and AVF outcomes.

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2. Trial Objectives, Design and Statistics

2.1. Trial objectives

The purpose of this RCT is to compare the efficacy of additional paclitaxel-coated balloon fistuloplasty versus plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

Primary Endpoint:

Time to end of target lesion primary patency

This is defined as patency with no re-intervention to the area 5mm proximal to, within, and 5 mm distal to, the index treatment segment. Target lesion primary patency ends when *any* of the following occur: (a) clinically driven re-intervention to the treatment segment; (b) thrombotic occlusion that includes 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 order to confirm there is a significant stenosis prior to fistuloplasty, Duplex ultrasound is encouraged but is not mandatory.

After the study treatment, occasionally there may be recoil or rupture necessitating further balloon angioplasty or stent placement. Providing further angioplasty and/or stent placement achieves a residual stenosis of less than 30%, these patients will remain in the study.

Referral for a repeat procedure will originate from the clinical team who are unaware of whether the patient received treatment with a paclitaxel-coated balloon or uncoated control balloon.

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 drug-coated balloon or placebo.

In order to ensure that there is no bias in the final decision to proceed with the repeat intervention in patients who have not yet reached the primary endpoint, pre-procedure fistulograms prior to potential re-intervention will undergo independent analysis. This will allow confirmation that a significant stenosis was found in all patients who received a repeat intervention.

Secondary Endpoints:

1. Angiographically determined late lumen loss.

This is the difference between the diameter of the treatment segment post-procedure and the diameter at 6 months as measured by an independent core laboratory. If a patient has a repeat procedure to the treatment segment before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

2. The rate of angiographic binary re-stenosis.

This is defined as the incidence of stenosis of at least 50% within the treated lesion at the 6 month follow-up fistulogram. If a patient has a repeat procedure to the index lesion before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

3. 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 access circuit is abandoned due to an inability to treat any lesion.

4. Time to end of access circuit cumulative patency

Access circuit cumulative patency ends 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.

5. Procedural success (residual stenosis ≤ 30% on completion fistulogram II, see section 4.4 below)

6. Number of thrombosis events

7. Total number of interventions

8. Adverse events (e.g. fistula rupture, infection)

9. Patient quality of life as assessed by the EuroQol EQ-5D generic health survey, and the disease specific Patient (or Palliative care) Outcome Scale symptom score-renal (POS-S Renal) [26].

2.2 Trial design

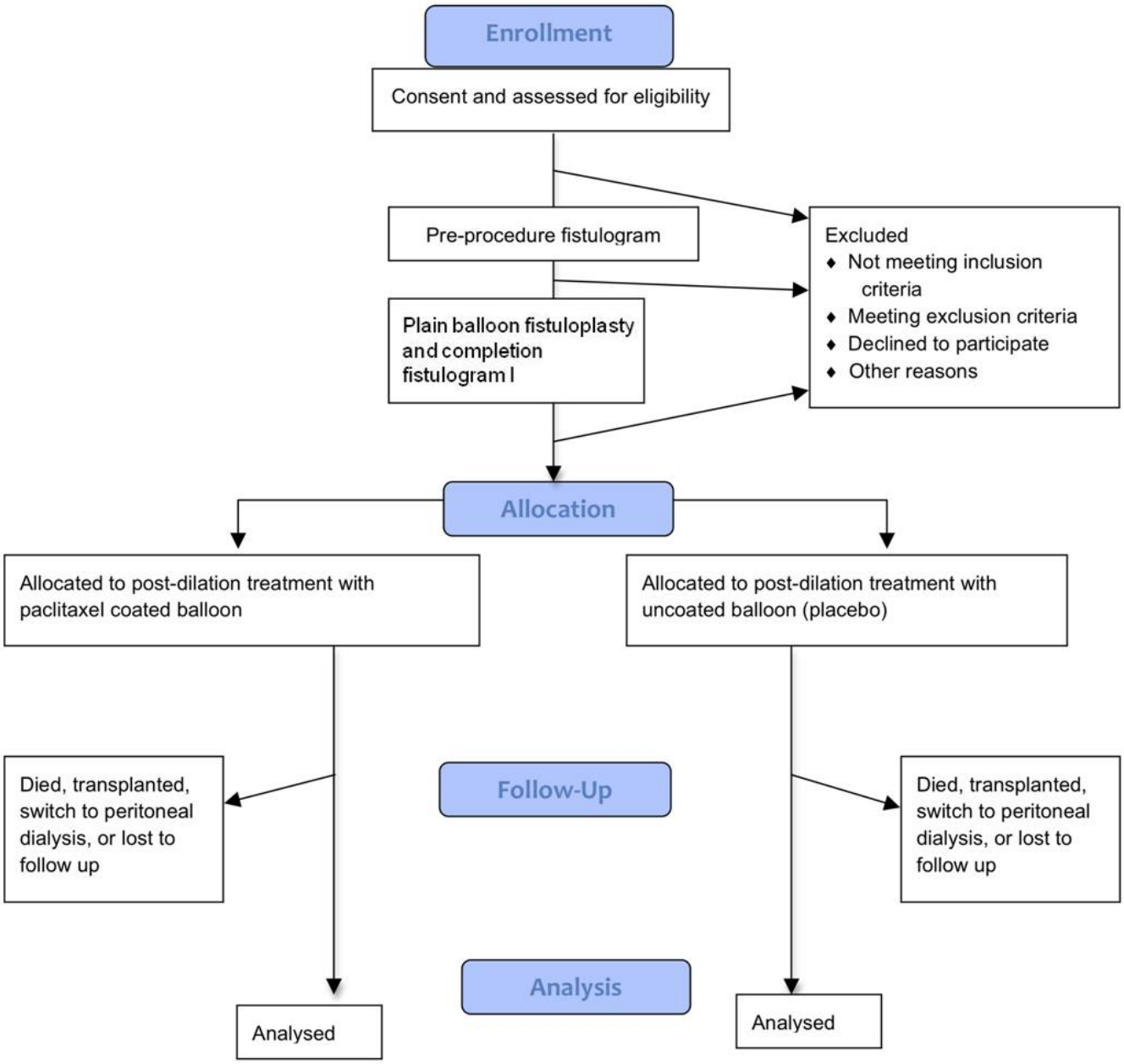
The study design used to achieve this will be a double-blind multicentre randomised controlled trial. We will recruit 211 patients over a two-year period. Patients will be followed up for a minimum of one year, and all patients will continue in the study until the last patient has completed one year of follow up.

2.3 Trial schedule

	Pre-procedure	Procedure	Post-procedure ****												
			Day 1-3	mth 3	mth 6	mth 9	mth 12	mth 15	mth 18	mth 21	mth 24	mth 27	mth 30	mth 33	mth 36
Patient registration and consent	x														
Medical history (including indication for fistuloplasty)	x														
Consideration of eligibility	x														
Discussion and confirmation of potential eligibility with radiologist	x														
Blood samples (taken on dialysis when possible)	x		x	x											
Pre-procedure fistulogram *		x													
Plain balloon fistuloplasty		x													
Completion fistulogram I *		x													
Randomisation		x													
Study treatment		x													
Completion fistulogram II		x													
Protocol fistulogram					x										
Follow up assessments ** ***				x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments (POS-S Renal and EQ-5D)	x				x		x								

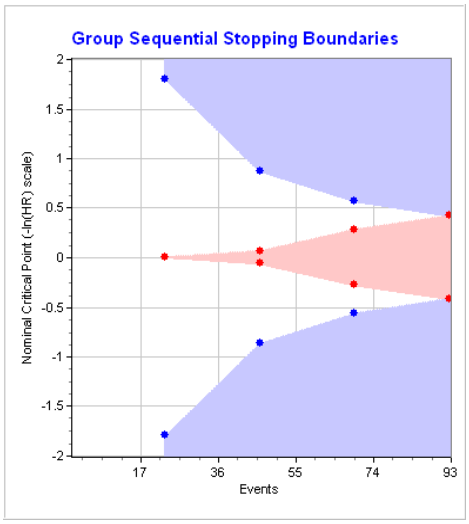
* Prior to randomisation, eligibility will be reviewed based on the radiological findings on both the pre-procedure fistulogram and completion fistulogram I
**At each follow up assessment information to be checked or collected will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events
***Follow up will be for a minimum of 12 months and a maximum of 36 months
****Post-procedure study assessments occur every 3 months ± 1 month; Day 1-3 blood sample to be taken at next dialysis session after procedure, if this falls on a weekend then blood to be taken at the next dialysis session after this

2.4 Trial flowchart



2.5 Trial statistics

Analysis of Primary Outcome: To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis. Primary analysis will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end. Kaplan-Meier plots, hazard-ratio and its confidence interval will be used to describe the results.



Analysis of Secondary Outcomes: Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate. Continuous variables will be checked for normality, transformed if necessary or otherwise analysed using a Wilcoxon-signed-rank test for independent samples.

Missing Values and Drop-outs: If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients lost to follow up will be compared to patients who reach complete follow up in baseline characteristics and adverse events to test whether drop-outs are random.

Interim Analysis: Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding.

3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results [7] and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size. Katsanos et al. [21] found a HR of 0.3 for TLPP at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, and recruitment of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

3.2 Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm
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. A reduction of vessel diameter of ≥ 50% measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon
5. A residual stenosis ≤ 30% after plain balloon fistuloplasty
6. A treatment segment, containing one or more lesions, which can be treated with ≤120 mm of a single drug-coated balloon.

3.3 Exclusion criteria

1. Patient unable to give informed consent
2. Patient unwilling or unable to comply with all study-related procedures
3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure
4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of ≥ 50% measured angiographically, in the same access circuit,
5. Location of stenosis central to the thoracic inlet
6. Thrombosed (failed) access circuit at time of treatment
7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment
8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated
9. Known hypersensitivity or contraindication to paclitaxel

3.4 Criteria for premature withdrawal

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

Participants will be withdrawn from the study if any of the following occur:

- Death of participant
- Participant receives a transplant
- Participant is changed from haemodialysis to peritoneal dialysis

The PI also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons, e.g. the participant is no longer being treated at a hospital included in the study.

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. Participants who wish to withdraw from 'treatment' will be asked to confirm whether they are still willing to provide study specific data and samples for scientific laboratory analysis according to the trial protocol.

4. Study Procedures

4.1 Screening procedures

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

In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory.

At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria as listed above in section 3 will be assessed. Inclusion criteria 1 and 2 will be confirmed and exclusion criteria 1-3 and 6-9 will be assessed.

The radiologist who will perform the pre-procedure fistulogram will be informed that the patient is potentially eligible for the study.

4.2 The pre-procedure fistulogram

This will be 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 following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
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. Measurement ruler in view
5. Lower arm acquisition to include:
    i. Anteroposterior Projection of anastomosis
    ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
    i. Peripheral (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Central reference vessel diameter

The radiologist will assess inclusion criteria 3 and 4, and exclusion criteria 4 and 5, to decide if the patient remains eligible for the study.

4.3 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 dedicated plain balloon (*Bard Dorado*). Only if the anatomy of the lesion precludes the use of the *Bard Dorado*, then an alternative high pressure balloon may be used, providing it has a rated burst pressure of >18 Atm. The following criteria will be met:

1. Sized to nominal vein diameter
2. Up to 24 Atm to ensure obliteration of the lesion waist
3. Minimum duration of balloon inflation 1 minute.

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
2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view

4. A core laboratory will make the following measurements at a later stage (these are not made by the radiologist performing the procedure)
    i. Peripheral (close to anastomosis) reference vessel diameter
    ii. Minimum lumen diameter (MLD)
    iii. Central reference vessel diameter

The radiologist will assess completion fistulogram I and decide if the residual stenosis is ≤ 30% (inclusion criterion 5). If this is the case the patient will proceed to randomisation, and if not the patient will be excluded.

4.4 Randomisation procedures

Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure, whether the participant is currently on haemodialysis or not, and whether the participant has had a previous radiological intervention in the access circuit or not. This is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically. This way, the next allocation will only be generated and become known upon actioning a request from the study site staff.

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 is currently on haemodialysis or not, and whether the participant has had a previous radiological intervention in the access circuit or not. 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.

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 with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

4.5 Study treatment

In the intervention arm, the second component is insertion of a single drug-coated balloon (*Bard Lutonix*). This must be of identical diameter to the plain balloon and a minimum of 1 cm longer than the plain balloon (5 mm at either end), inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

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 single placebo balloon that is not drug coated (*Bard Ultraverse*). This must be of identical diameter to the plain balloon and a minimum of 1 cm longer than the plain balloon (5 mm at either end), inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

If more than one plain balloon is used for the plain balloon fistuloplasty then the dimensions of the placebo balloon (*Bard Ultraverse)* *or* drug-coated balloon (*Bard Lutonix*) is matched to the plain balloon with the larger diameter and/or the longer length.

In both arms, image overlay/roadmap will be utilized to ensure that there is no geographical mismatch between the segments treated with the high and low-pressure balloons.

A completion fistulogram is performed (completion fistulogram II) to confirm no angiographically visible effect after treatment with the drug-coated or placebo balloon, according to the same specifications as fistulogram I in section 4.3. Procedural success is defined as a residual stenosis ≤ 30% on completion fistulogram II.

The data file(s) containing the initial pre-procedure fistulogram, and completion fistulogram I and II will be sent to the lead study site with the patient's name replaced by the trial ID, and with each of the above groups of images clearly identified. Completion fistulogram II will then be sent to the independent angiographic laboratory for analysis.

4.6 Study assessments

These will occur every 3 months ± 1 month. Follow up will be variable but for a minimum of 1 year and will continue for each patient while the study remains open. It is expected that the study will remain open for 3 years. These will involve a clinical assessment to 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.

Data recorded for each study assessment will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, patient medications, and adverse events.

At the 6 month study assessment, the trial team will additionally collect information on fistula function and check if referral for re-intervention is being considered based on clinical concerns. If this is the case then a fistulogram ±plasty will be performed according to usual clinical practice and the patient will not undergo a protocol fistulogram. If there are no clinical concerns related to the fistula, then patients will be invited to undergo a protocol fistulogram. The decision to perform a protocol fistulogram or not to, will be confirmed with the PI after discussion with relevant clinical colleagues.

4.7 Radiology Assessments

4.7.1 The 6 month protocol fistulogram

This will take place within 6 weeks of the 6 month study assessment.
Patients may be reimbursed for travel costs for this.

If a patient has required a repeat fistuloplasty to the treatment segment at or before 6 months then they will not undergo the 6 month protocol fistulogram.

All other patients will be invited to undergo a protocol fistulogram 6 months after the index procedure to acquire the data for the angiographic secondary endpoints. If a patient declines the 6 month protocol fistulogram or does not have it for another reason, this will not be considered a protocol violation and the patient may continue in the study.

The 6 month protocol fistulogram *must* be performed by a radiologist other than the one who performed the index procedure to ensure that they are blind to which trial arm the participant belongs. With forward planning this should be possible but if it is not then the protocol fistulogram should not be performed.

The 6 month protocol fistulogram will be a diagnostic study only unless an unsuspected stenosis is found and the radiologist believes that it would be unethical not to intervene. This will not be considered a protocol violation and a fistula intervention form will need to be completed. The 6 month protocol fistulogram will follow the same specifications as the pre-procedure fistulogram in section 4.2.

The 6 month protocol fistulogram will be considered to be exclusively trial data. The result of the 6 month protocol fistulogram will not be made available (verbally or in writing) to the clinical team responsible for considering future referral of the patient for an intervention. The images will also not be available on the local radiology system. The images will be sent to the lead site in order to be forwarded to the independent core laboratory with the patient's name replaced by the trial ID.

4.7.2 Fistulograms performed for a clinical indication

In patients who have not yet reached the primary endpoint of the trial, pre-procedure fistulograms will follow the same specifications as the pre-procedure fistulogram specifications in section 4.2. The image file will be sent to the lead site with the patient details replaced by the trial PIN. This will be sent regardless of whether or not the fistulogram is followed by a fistuloplasty.

In patients who undergo an intervention, before 6 months, to the treatment segment, the pre-procedure fistulogram will be used (by the independent core laboratory) in place of the 6 month protocol fistulogram for analysis of the angiographic secondary endpoints.

4.8 End of Study Definition

The clinical trial will end when 211 patients have been recruited and all patients have completed at least one year of 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.

5. Laboratories

5.1 Laboratory tests

There are no local laboratory tests that are required to provide data that directly relate to trial endpoints. A 10 ml blood sample will be requested at the four timepoints stated in the trial schedule (2.3), and is to be sent to the local clinical laboratory for a full blood count and to check the C-reactive protein level. If patients decline some or all of these samples, it will not be considered a protocol violation.

Blood (up to 90 ml) may be taken at each of the time points in the table of events in 2.3. These will be sent to the research laboratory of the CI where the blood will be separated. Research blood samples

should not be taken from patients who are known to be hepatitis B sAg, hepatitis C IgG/ RNA, or HIV positive. DNA and RNA will be stored. Cells will be stored in aliquots in liquid nitrogen until thawed for analysis. Serum and/or plasma samples will be stored at -20'C or -80'C until thawed for analysis. Transport, separation and storage will be according to Standard Operating Procedures. It will not be a considered a protocol violation if any of the blood samples are not taken, or are taken at different time points to those specified and patients may continue on the study.

If a patient is enrolled but not randomised, the patient will not continue in the clinical trial. However blood samples may continue to be taken for laboratory research (at the same time points as for patients remaining in the trial). Clinical data may also be recorded though this may not be on the eCRF system.

5.2 Independent Core Lab Analysis

The completion fistulogram II (taken after treatment with the DCB or placebo low pressure balloon) will be compared with the protocol 6 month fistulogram or with the pre-procedure fistulogram taken prior to a clinically driven re-intervention at the treatment segment if this is before 6 months. These will be analysed by an Independent Core Lab for the angiographic secondary endpoints.

In addition, in patients who have not yet reached the primary endpoint of the trial, clinically-driven pre-procedure fistulograms will be sent to the Independent Core Lab for analysis if they were performed by a radiologist who is not blind to the study treatment. This will be sent regardless of whether the fistulogram is followed by a fistuloplasty.

6. Assessment of Safety

We have been informed by the MHRA that the PAVE 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.

All SAEs 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. A planned or non-elective hospital admission does not need to be reported as an SAE unless the PI decides it should be.

Although it is not an SAE, any pregnancy or fathering of children that occurs within 2 years of the study treatment will be reported via the SAE system as below.

Reports of SAEs will be reviewed by the CI within 24 hours to assess whether 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, in the format prescribed by NRES and published on the website.

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 vascular access that has been treated. These should be recorded throughout the trial and will be captured in the eCRF at each study assessment.

7. 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 or by telephone. They will report to the TSC who will usually meet in the two weeks following the DMC meeting. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. 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.

8. Trial Steering Committee

The TSC will be convened in the post-award period. The membership will be decided by the CI and approved by the NIHR. The chair will be an independent expert. Members will include the CI, a patient representative, and two other independent experts. The TSC will meet at least annually during the study, approximately 2 weeks after the DMC. 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.

9. Ethics & Regulatory Approvals

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.

This protocol and related documents will be submitted for review to the London-Chelsea Research Ethics Committee (REC).

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.

10. Data Handling

All samples will be anonymised before laboratory analysis. No patient-related data will be held in research laboratories.

During the study, any paper documents 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.

Clinical and research data for the study will be stored on the eCRF system, hosted at the King's Clinical Trials Unit, KCL. 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.

11. Publication Policy

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.

12. Insurance / Indemnity

The study will be indemnified by King's College London for negligent and non-negligent harm. In addition, the recruiting sites will have NHS indemnity.

13. Financial Aspects

The NIHR have supported the study through an EME programme grant award. The fistuloplasty balloons are supplied by C.R. Bard, Inc. who have no other role in the design, running, or analysis of the trial.