PAVE Statistical Analysis Plan

# 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 stenosis in haemodialysis access

Statistical Analysis Plan

Version 2.0

Version 2.0 started: 26/09/2018

ISRCTN: 14284759

This SAP has been written based on Protocol V8.0

Trial Statistician: Emily Robinson

Signature Date 15/11/2018

Chief Investigator: Dr Michael Robson

Signature Date 14/05/2019

Trial Steering Committee Chair: Dr Richard Haynes

Signature Date 15/11/2018

Data Monitoring Committee Statistician: Dr Isabel Reading

Signature: Date: 01/11/2018

PAVE Statistical Analysis Plan

# Contents

PAVE Statistical Analysis Plan

# 1 QUANTITATIVE ANALYSIS PLAN

This document details the presentation and analysis strategy for the primary paper reporting results from the PAVE trial. Subsequent papers of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the principle paper(s). The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices. Rather, they are intended to establish the primary scientific objective of the study, including the primary comparison and primary outcome and the strategy that will be followed as closely as possible, when analysing and reporting the trial.

**Investigators**
Mr Keith Brennan
Dr Kate Blake
Dr Michael Robson
Dr Narayan Karunanithy
Mr Francis Calder

**Principal investigator**
Dr Michael Robson

**Trial managers**
Dr Leanne Gardner
Ms Michaela Curran

**Trial statisticians**
Dr Yanzhong Wang
Miss Emily Robinson

## 1.1 Description of the trial

This is a double-blind, multicentre RCT to assess the efficacy of additional paclitaxel-coated balloon angioplasty compared to high-pressure balloon angioplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

### 1.1.1 Principal research objectives to be addressed

The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.

**Primary objective**
To assess time to end of target lesion primary patency (TLPP) following study treatment angioplasty.

**Secondary objectives**
To assess the difference between the two groups in:

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. Number of fistula interventions
8. Adverse events
9. Patient quality of life assessed by EQ-5D and POS-S Renal

A detailed description of trial objectives can be found in protocol section 2.1.

### 1.1.2 Trial design including blinding

The study is a double-blind multicentre randomised controlled trial, aiming to recruit 211 patients over a two-year period. Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure; whether the patient has had a previous radiological intervention in the access circuit or not; and whether the patient is currently on haemodialysis. Follow up will be variable and 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.

### 1.1.3 Method of allocation of groups

Recruitment and pre-screening procedures are described in the protocol sections 4.1-4.3. Once the patient has completed the pre-procedure fistulogram, high-pressure balloon fistuloplasty, and the completion fistulogram I, the radiologist will assess if the residual stenosis is ≤30%; if this is the case then the patient will proceed to randomisation.

Randomisation will take place via a web based randomisation service, 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 performing the study procedure, or their nominee, and each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

As explained in 1.1.2, patients will be randomized using minimisation; this is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically so that the next allocation will only be generated and become known upon actioning a request from the study site staff. Once randomised, the system will automatically generate an email confirmation, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study: an unblind email is received by the trial manager and the radiologist who is performing the randomisation; and a blind email is received by the principal investigator and research nurses.

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.

### 1.1.4 Duration of the treatment period

Study treatment is described in detail in the protocol section 4.5. This is a one-off treatment that is administered within one study visit. Any repeat intervention is considered an event and therefore the end of the follow up.

### 1.1.5 Frequency and duration of follow-up

Study assessments will take place every 3 months. Follow up will be variable but for a minimum of 1 year. 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.

### 1.1.6 Visit windows

At the time of each 3-month study assessment, an allowance of one month will be given either side to measure follow-up. This one month visit window will be the same for recording data throughout the follow-up period.

### 1.1.7 Eligibility screening

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 will be assessed.

Inclusion and exclusion criteria are described in sections 3.2 and 3.3 of the protocol.

The radiologist who will perform the pre-procedure fistulogram, high-pressure balloon fistuloplasty and completion fistulogram will be informed that the patient is potentially eligible for the study, and they will assess the remaining eligibility criteria.

### 1.1.8 Measures

**Baseline**
The following demographics will be measured at baseline:

- Age (years)
- Gender (male; female)
- Ethnicity (White; Black; Asian; Mixed; Other)

The following clinical details will be measured at medical history screening:

- Current diabetes diagnosis (yes; no)
- Patient smoking history (current smoker; former smoker; never smoked)
- Coronary artery disease (yes; no)
- Peripheral vascular disease (yes; no)
- Time since end-stage kidney failure (months)
- Previous renal transplant(s) (number)
- Total accumulated time with a functional renal transplant (months)
- Total accumulated time patient has spent on haemodialysisis (months)
- Total accumulated time patient has spent on peritoneal dialysis (months)
- Location of fistula (right arm; left arm)
- Type of native fistula (Radio-cephalic; Brachio-cephalic; Basilic vein transposition; Ulnar-cephalic)
- Time since fistula was formed (months)
- Time since fistula was first used (months)
- Current access circuit previously had a thrombosis (yes; no)
- Previous surgical interventions to the current access circuit (number)
- Previous fistuloplasties to the current access circuit (number)
- Primary indication for the index procedure (inadequate dialysis; poor fistula blood flow; prolonged bleeding; high venous pressures; low arterial pressure; difficulty needling; other evidence of fistula dysfunction)

The following clinical details will be measured at the pre-procedure fistulogram:

- Location of stenosis (juxta-anastamotic; venous segment; cephalic arch; after cephalic arch and not beyond the thoracic inlet; beyond the thoracic inlet)
- Degree of stenosis (5%)
- Length of stenosis (mm)
- Radiologist (initials)

The following clinical details will be measured at the treatment fistuloplasty:

- Index lesion vessel diameter (mm)
- Diameter of plain balloon used (mm)
- Length of plain balloon used (mm)
- Pressure to which used plain balloon was inflated (atm)
- Number of unsuccessful attempts at plain balloon fistuloplasty (0-2)
- Complications due to plain balloon fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Diameter of study treatment balloon used (mm)
- Length of study treatment balloon used (mm)
- Pressure to which study treatment balloon was inflated (atm)
- Complications of the study treatment fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Residual stenosis still 30% or less after study treatment (yes; no)

- Further fistuloplasty performed after study treatment (yes; no)
- Type of balloon from further fistuloplasty (Dorado; other)
- Diameter of balloon from further fistuloplasty (mm)
- Length of balloon from further fistuloplasty (mm)
- Residual stenosis 30% or less after further fistuloplasty (yes; no)
- Complications due to further fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Radiologist (initials)

**Primary outcome measures**
The primary outcome measure is time to Target Lesion Primary Patency (TLPP). This will be measured in days post treatment fistuloplasty.

**Secondary outcome measures**
The secondary outcomes, as listed in 1.1.1, will be measured as follows:

1. Late lumen loss (mm); the difference between the diameter of the lesion at the completion fistulogram II (baseline) and at the protocol fistulogram (6 months)
2. Rate of binary angiographic re-stenosis (%); at the protocol fistulogram (6 months)
3. Time to loss of access circuit primary patency (days post treatment fistuloplasty)
4. Time to loss of access circuit cumulative patency (days post treatment fistuloplasty)
5. Procedural success (yes; no); stenosis ≤30% at completion fistulogram II (baseline)
6. Thrombosis events (number); recorded as fistula interventions throughout the trial
7. Fistula interventions (number); recorded throughout the trial
8. Adverse events (number); recorded throughout the trial
9. Patient quality of life; EQ-5D and POS-S Renal scores

**Adverse events**
The following adverse event measures will be collected at 6 and 12 months post randomisation, and at withdrawal, where applicable:

- Adverse Event (Oedema of hand or arm; Pseudoaneurysm; Haematoma; Distal Ischaemia; Neurological complications; Infection localised to fistula; Central venous catheter insertions; other)
- Duration of event (days)
- Intensity (mild; moderate; severe)
- Outcome (resolved; resolved with sequelae; ongoing; death; unknown)
- Related to study intervention (definite; probable; possible; remote; none)
- Serious Adverse Event (yes; no)
- Ongoing at end of study (yes; no)

Please refer to section 2 for the schedule of assessments and measures.

### 1.1.9 Sample size estimation (including clinical significance)

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 (Bountouris, 2014; Tessitore, 2003) and with our own audit

data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size; (Katsanos, 2012) found a HR of 0.3 for Target Lesion Primary Patency 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, 66 in the control arm, and 42 in the intervention arm.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, which would result in 6 patients in the treatment arm, and 3 in the control arm. We have planned for a recruitment rate 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.

### 1.1.10 Brief description of proposed analyses

Analyses will be carried out by the trial statistician (ER) once the database has been locked. Data will be analysed with an intention-to-treat approach (i.e. analyse all those with data in groups as randomised irrespective of treatment received).

There will be descriptives statistics reported on the measures mentioned in 1.1.8, with an aim to comparing the treatment arms, and to review the patient demographics.

For the primary analysis, to test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival, Cox-Proportional Hazards regression will be used. This will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates; which are listed in detail in section 1.3.2.

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.

Interim analysis of the primary outcome will be performed up to three times throughout the study, based on the cumulative number of failures of the treatment area.

Further details of the analyses are given later on in this document.

Data summaries and analyses will be carried out in Stata 14.0.

## 1.2 Data analysis plan – Data description

### 1.2.1 Recruitment, eligibility and representativeness of patients

A CONSORT flow chart will be constructed – see Figure 1. The number of patients will be summarised using the following categories: total number of patients screened; eligible; consenting; and randomised.

Then by treatment arm: patients compliant and non-compliant with intervention; continuing through the trial; withdrawing; lost to follow-up; and excluded or analysed.

Compliance (adherence) is defined as receiving the following procedures: plain balloon fistuloplasty; completion fistulogram I; study treatment fistuloplasty; and completion fistulogram II.

A summary of the number of patients compliant with the study treatment will be provided and stratified by radiologist.

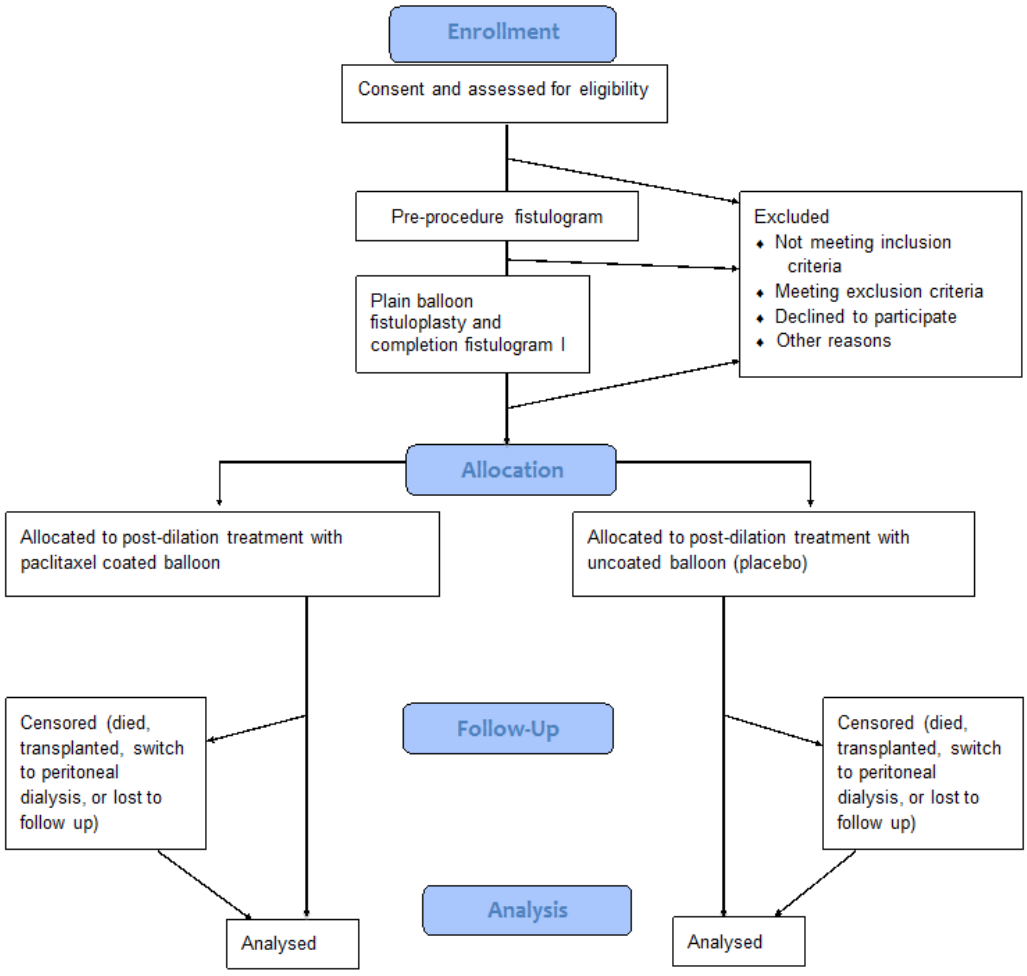



Figure 1. Template CONSORT diagram for PAVE trial

### 1.2.2 Baseline comparability of randomised groups

All baseline variables listed under measures in section 1.1.8 will be reported by trial arm and overall. They will be grouped into patient demographics and patient clinical information, and reported as: minimums and maximums, means and standard deviation, medians and quartiles for continuous variables as appropriate; and frequencies and proportions for categorical variables. No significance testing will be used to test baseline differences between the trial arms.

### 1.2.3 Adherence to allocated treatment and treatment fidelity

Adherence to allocated treatment (compliant versus non-compliant), as described in 1.2.1, and the reasons for not completing the treatment process will be summarised using the treatment fistuloplasty form. Adherence will be compared between trial arm using baseline variables; and the reasons for withdrawal from treatment will be summarised.

### 1.2.4 Loss to follow-up and other missing data

Withdrawal from trial follow-up (attrition rate) will be reported by intervention group, including reasons for withdrawal. The proportions of participants missing each variable will be summarised in each arm and at each study visit.

If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. 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.

The baseline characteristics and adverse events of patients lost to follow up will be compared to those with complete follow up data. The relationship between these and missing data will be investigated graphically to see if baseline characteristics or adverse events predict missing, i.e. drop-outs are not random.

### 1.2.5 Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by trial arm and overall.

### 1.2.6 Assessment of outcome measures (unblinding)

Outcome assessors and the trial statistician are being kept blind to treatment allocation.

### 1.2.7 Descriptive statistics for outcome measures

The primary and secondary outcomes as listed in section 1.1.8 will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables, where relevant; this will check whether continuous outcomes can be assumed normally distributed. Kaplan-Meier plots,

hazard-ratio and its confidence interval will be used to describe the time to event results. Frequencies and proportions will be used to describe binary variables.

## 1.3 Data analysis plan – Inferential analysis

### 1.3.1 Aims of formal inferences

The formal statistical analyses will estimate the differences in relevant variables (time to event, quality of life) between patients randomised to the paclitaxel-coated balloon angioplasty compared to high-pressure placebo balloon angioplasty, by intention to treat.

As mentioned in section 1.2.4, for the primary outcome and other time to event variables, patients lost to follow-up will be right censored; this means they are counted as not having experienced end of target lesion primary patency, or the relevant event, for the period of time we have data on them. If dropout is related to both outcome and treatment, then dropouts may bias the results.

Group difference estimates and associated 95% confidence intervals will be reported. The trial statistician will remain blind until the main analyses have been completed. The overall significance level will be 5% (two-sided) for the primary and secondary outcomes. Significance level of final analysis of primary outcome will be determined by the alpha spending function used to plan interim analyses.

Details on the methods for handling missing data are given in sections 1.3.8.

Sensitivity analyses will be used to assess the robustness of conclusions; please refer to section 1.4 for details of the planned sensitivity and subgroup analyses.

### 1.3.2 Analysis of the primary outcome

The analysis population will include all patients randomised with sufficient information to carry out the analysis, i.e. complete primary outcome data and minimisation factors. The primary outcome is time to end of target lesion primary patency (TLPP); measured as days post randomisation. For the purpose of the primary outcome analysis, this will be taken as recorded by the target lesion primary patency form.

Expected time to end of TLPP will be calculated using the hazard ratio estimated by the model explained below. Survival analysis methods will be used to compare the primary outcome for the two groups as this can factor in censoring and time.

Kaplan-Meier plots will be used to graphically illustrate and compare the observed probabilities of target lesion primary patency past certain times in the trial period, taking into account censoring, for the two trial arms. This is a non-parametric estimate of the survival function over the analysis time, and will also be used to check the Cox proportionality assumption – see section 1.3.10.

Cox-Proportional Hazards regression will be used to model the effect of predictors and covariates on the hazard rate and estimate the relative risk by trial arm. This will be compared to an initial estimate from the null model where the model will be fitted without any covariates. Model components included in the primary model will be a baseline hazard function that is unspecified but positive; previous radiological intervention in the access circuit; on haemodialysis at randomisation; trial arm; observed study time (length of time between patient entering and exiting study); and a trial arm*observed time interaction term. The interaction term allows for variable follow-up time effects.

A secondary adjusted analysis will be fit to evaluate the impact of baseline covariates on the size of the treatment effect. The covariates considered will be: baseline characteristics (ethnicity; age; diabetes diagnosis; and smoking history) and clinical variables at baseline (total time on haemodialysis; time since end stage kidney failure; type of native fistula; previous circuit intervention; and location of stenosis).

The relationship between baseline variables and missing outcome data will be assessed using logistic regression with an outcome variable that represents whether outcome data are present or missing. Should any baseline variables be predictive of missing then these will be included in the primary analysis Cox regression models as further covariates.

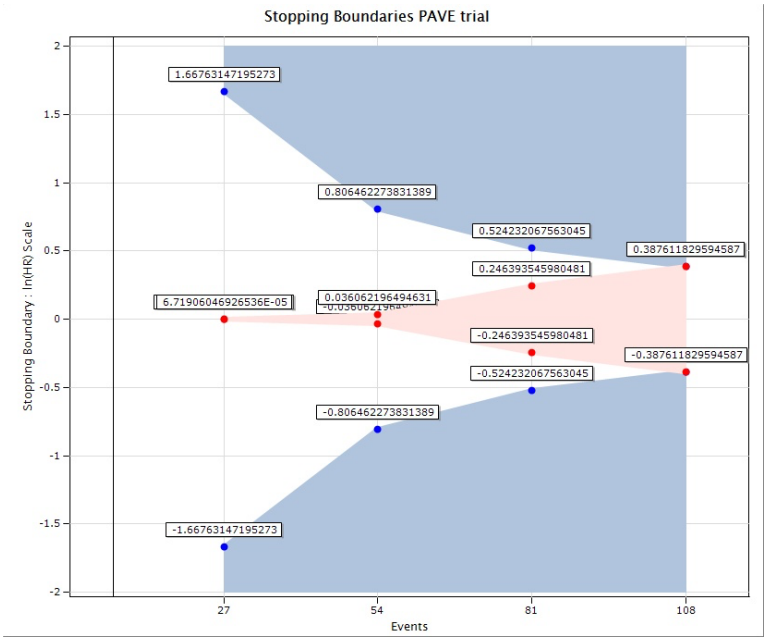
### 1.3.3 Interim analysis

Interim analysis of the primary outcome will be performed up to three times throughout the study, based on the cumulative number of failures in the primary outcome, 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 hypothesis. 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 and will be discussed with the DMEC members during a closed session that does not include any trial members who are blinded.

The Hazard Ratio used to evaluate the crossing of stopping boundaries will be calculated with a Cox-proportional hazards regression that includes presence or absence of previous interventions and currently on haemodialysis or not as covariates, as well as treatment group as independent variable of interest.

Stopping boundaries are displayed in the figure below:

# PAVE Statistical Analysis Plan




The table below shows further details of the stopping boundaries, including expected probability of crossing at each interim, and cumulative Alpha and Beta spent. Stopping boundaries in the table are expressed in the HR scale.

| Look # | Info. Fraction | Events | Cum. α Spent | Cum. β Spent | Boundaries | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Efficacy Boundary | | Futility Boundary | |
| | | | | | Upper | Lower | Upper | Lower |
| 1 | 0.25 | 27 | 0 | 0 | 5.3 | 0.189 | 1 | 1 |
| 2 | 0.5 | 54 | 0.003 | 0.004 | 2.24 | 0.446 | 1.037 | 0.965 |
| 3 | 0.75 | 81 | 0.019 | 0.024 | 1.689 | 0.592 | 1.279 | 0.782 |
| 4 | 1 | 108 | 0.05 | 0.059 | 1.473 | 0.679 | 1.473 | 0.679 |

| Look # | Sample Size | | Analysis Time | | Incremental Boundary Crossing Probabilities | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Under H0: ln(λ_t/λ_c) = 1 | | | Under H1: ln(λ_t/λ_c) = 0.49... | | |
| | Under H0 | Under H1 | Under H0 | Under H1 | Efficacy | | Futility | Efficacy | | Futility |
| | | | | | Upper | Lower | | Upper | Lower | |
| 1 | 91 | 106 | 9.483 | 10.968 | 0 | 0 | 0 | 0 | 0.006 | 0 |
| 2 | 140 | 163 | 14.522 | 16.985 | 0.002 | 0.002 | 0.105 | 0 | 0.333 | 0.004 |
| 3 | 185 | 211 | 19.213 | 22.651 | 0.008 | 0.008 | 0.633 | 0 | 0.44 | 0.02 |
| 4 | 211 | 211 | 23.95 | 33.792 | 0.014 | 0.014 | 0.214 | 0 | 0.162 | 0.035 |

Test statistics for interim analysis will be calculated with standard statistics software packages (R or Stata).

Interim analyses will be programmed by the trial statistician, and run and using the partially blinded randomisation sequence (trial arm numbers 1 or 2). The results will be presented to the DMEC in a partially blind report, and full unblinding of the code will only be provided to the members if they request it.

### 1.3.4 Analysis of secondary outcomes

Secondary patient outcomes relating to time-to-event variables, for example, time to end of access circuit primary patency, will be analysed using Cox regression models in a similar method to above.

Continuous variables such as POS-S Renal score for quality of life, will be checked for normality, transformed if necessary and analysed using linear regression models. Otherwise, they will be analysed using a Wilcoxon-signed-rank test for independent samples. Logistic regression models will be used for binary secondary outcomes, for example, procedural success (rate of binary angiographic re-stenosis ≥50%) at the six month protocol fistulogram.

Similarly to the primary outcome analysis, covariates considered in the models will include: baseline measure of outcome variable, where applicable; minimisation factors; trial arm; and time in study. An interaction term will also be included between observed study time and study treatment, as above.

### 1.3.5 Stratification and clustering

Randomisation is on the patient level, minimising on radiologist performing the study treatment and previous radiological intervention to treatment area or not; therefore these variables will be included as covariates in the modelling process, as mentioned in section 1.3.2. However, the data should not have a clustered structure so this does not need to be accounted for.

### 1.3.6 Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales.

### 1.3.7 Missing baseline data

We do not anticipate missing values in pre-randomisation variables. However, if we encounter missing baseline values then these can be singly imputed without incurring bias of the treatment effect estimate (White & Thompson, 2005).

### 1.3.8 Censoring and missing outcome data

For time to event outcomes, patient data is considered censored when the patient is withdrawn from follow-up, i.e. it is only known that the amount of time to event for that patient is greater than some value. Censoring will also happen at the end of the study, if the patient does not experience the primary endpoint before end of follow-up. In the analysis,

the censored observations will be included in the number of patients at risk in respect to their observed study time (survival time).

For non-time to event outcomes, missing post-randomisation assessments will be dealt with by fitting generalised linear models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR). This allows for missingness at later times to be predicted by outcome values at earlier times. However, if post treatment variables such as compliance with study procedures are found to be predictive of drop out, multiple imputation will be considered.

### 1.3.9 Method for handling multiple comparisons

Analysis of secondary outcomes is considered exploratory, and therefore there will be no correction for multiple testing. However, care should be given to the interpretation of inference for the numerous secondary outcomes and it may be necessary to assess the agreement between similar outcome measures. Cohen's Kappa statistic and/or Spearman's rank correlation coefficients may be used to test for inter-participant reliability and to measure the degree of linear association between two outcomes. For example, angiographically determined late lumen loss and the rate of binary angiographic re-stenosis would be expected to be highly predictive of one another.

### 1.3.10 Method for handling non-compliance

In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated.

There is not expected to be a problem with non-compliance due to the design of the trial.

### 1.3.11 Model assumption checks

In order to assess the adequacy of the Cox regression models for the primary outcome and time-to-event secondary outcomes, the main assumption to test for is proportionality; the Kaplan-Meier plots will be used to check if the curves for the two trial arms are the same shape, and if the separation of the curves remains proportionate throughout the analysis period.

In addition, time-dependent covariates will be generated by creating interactions of the predictors and function of survival time; if these are significant then the predictors are not proportional.

If the assumption for proportionality is violated then the consequence this has on the results can be checked. The Cox model can be stratified according to the variables with non-proportional hazards to see whether that changes the hazard ratios for the variables of interest; if it still does, then it may be necessary to use an alternative model. One parametric alternative is the Royston-Parmar model, which is more flexible and can fit a non-proportional hazards model.

For the other secondary outcomes regression residuals will be plotted to check for normality and outliers, where applicable.

## 1.4 Sensitivity analyses

### 1.4.1 Planned sensitivity analyses

A sensitivity analysis will be performed using adjudicated data from the core lab readings, in comparison to the primary analysis where the events reported in the trial will be used. This will assess the robustness of the trial findings by clarifying whether the primary analysis conclusions are impacted by any methodological issues, such as outcome definitions.

### 1.4.2 Planned subgroup analyses

Subgroup analyses will be carried out to assess whether the observed effect is consistent across patient categories; to do this, an interaction term will be included in the Cox proportional hazards model between the exposure (study treatment group) and the subgroup variable.

The planned subgroups will be: second minimisation factor (previous radiological intervention to the treatment area or not); smoking history (current smoker, former smoker, never smoked); baseline diabetes diagnosis (yes, no); current total time on haemodialysis (quartiles); total time since end stage kidney failure (quartiles); type of native fistula (Radio-cephalic, Brachio-cephalic, Basilic vein transposition, Ulnar-cephalic); and location of stenosis (juxta-anastomotic, venous segment, cephalic arch, between cephalic arch and thoracic inlet).

### 1.4.3 Competing risks analyses

To assess the influence of events that may prevent other events from being observed, competing risks analyses will be planned to adjust for these. Specifically, 'irrelevant' deaths and re-transplantations will be defined as competing risks rather than censored events. The cause of death will be checked from hospital notes and/or death certificates.

### 1.4.4 Exploratory analyses

This analysis plan does not cover secondary exploratory analysis. Exploratory mediator and moderator analyses may be performed after the primary trial data analysis.

## 1.5 Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at KCL and managed by the KCTU. The KCTU Data Manager will extract data periodically as needed and requests will usually be made by the trial statistician. There will be several database extracts throughout the trial for each DMEC Report, and a final extract after data lock. Data will be provided in comma separated (.csv) format.

Statistical analysis: Stata and or R will be used for data description and inferential analysis.

## 1.6 Changes to version

1 Since Version 1.0 the Trial Manager(s) have changed, and this has been updated
2 Due to the recruitment period taking longer than planned, and including more hospital sites than originally expected, clarification has been made to the following sections in relation to minimisation factors, duration of trial follow-up, and frequency of interim analysis:
- 1.1.2
- 1.1.5
- 1.1.6
- 1.1.10
- 1.2.1
- 1.3.2
- 1.3.3
- 1.3.8

## 2 SCHEDULE OF ASSESSMENTS AND MEASURES

| PAVE | Variable count | Enrolment | Treatment day (Day 0) | Day 1-3 | Month 3 | Month 6 | Month 9 | Month 12 | Month 15 | Month 18 | Month 21 | Month 24 | Month 27 | Month 30 | Month 33 | Month 36 | Ongoing |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 01. Registration form | 5 | X | | | | | | | | | | | | | | | |
| 02. Eligibility form | 14 | X | | | | | | | | | | | | | | | |
| 03. Medical History form | 19 | X | | | | | | | | | | | | | | | |
| 04. Haematology and Biochemistry form | 11 | X | | X | X | X | | | | | | | | | | | |
| 05. Pre-procedure Fistulogram form | 8 | | X | | | | | | | | | | | | | | |
| 06. Randomisation form | 4 | | X | | | | | | | | | | | | | | |
| 07. Treatment Fistuloplasty form | 46 | | X | | | | | | | | | | | | | | |
| 08. Fistula Intervention form (repeating) | 32 | | | | | | | | | | | | | | | | X |
| 09. Month 6 Fistula Function form | 9 | | | | | X | | | | | | | | | | | |
| 10. Protocol Fistulogram form | 11 | | | | | X | | | | | | | | | | | |
| 11. POS-S Renal questionnaire | 25 | X | | | | X | | X | | | | | | | | | |
| 12. EQ-5D questionnaire | 6 | X | | | | X | | X | | | | | | | | | |
| 13. Medications form | 17 | X | | | X | X | X | X | X | X | X | X | X | X | X | X | |
| 14. Adverse Events form | 9 | | | | | | | | | | | | | | | | X |
| 15. Withdrawal form | 5 | | | | | | | | | | | | | | | | X |
| 16. Status form | 5 | | | | X | X | X | X | X | X | X | X | X | X | X | X | |
| 17. Loss of Patency form (repeating) | 9 | | | | | | | | | | | | | | | | X |

# 3 References

1. Bountouris I, Kristmundsson T, Dias N, Zdanowski Z, Malina M. Is Repeat PTA of a Failing Hemodialysis Fistula Durable? Int J Vasc Med. 2014; 2014: 369687.
2. Katsanos K, Karnabatidis D, Kitrou P, Spiliopoulos S, Christeas N, Siablis D. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial. J Endovasc Ther. 2012 Apr;19(2):263-72.
3. Tessitore N, Mansueto G, Bedogna V, Lipari G, Poli A, Gammaro L, Baggio E, Morana G, Loschiavo C, Laudon A, Oldrizzi L, Maschio G. A prospective controlled trial on effect of percutaneous transluminal angioplasty on functioning arteriovenous fistulae survival. J Am Soc Nephrol. 2003 Jun;14(6):1623-7.
4. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Stat Med. 2005 Apr 15;24(7):993-1007.