VERSION CONTROL DOCUMENT – keep at front of Trial Master File

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Study Title (full):	Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access		
Study Title (short):	PAVE		
Study Rec ref:	15/LO/0638	**Chief Investigator:**	Dr Michael Robson

PROTOCOL

VERSION No.	DATE	DATE APPROVED BY ETHICS	Changes
2.0	21 / 07 / 2015	18 / 08 / 2015	Version 2 it was approved and live before the first site opened to recruitment.
3.0	20 / 10 / 2015	03 / 11 / 2015	Wording in the protocol describing trial procedures have been changed for clarification: • "high pressure" changed to "plain" when describing the balloon used in the initial procedure • "treatment area" changed to "treatment segment" • The stratifier "whether or not the participant has had a previous intervention to the treatment segment" has been changed to "whether or not the participant has had a previous intervention in the access circuit" • The definition of the primary endpoint has been changed from "this is defined as patency with no reintervention to the area 5mm proximal within, and 5 mm distal to, the index treatment segment" to "this is defined as patency with no reintervention to the area 5mm proximal to, within, and 5 mm distal to the index treatment segment" It has been clarified in inclusion criteria 1 that eligible participants should have an AVF that has been in use for 12 "consecutive" dialysis sessions (also listed in IRAS QA171) An additional secondary endpoint, "total number of interventions" has been added (also listed in IRAS QA11). The treatment procedure has been further clarified to ensure uniformity over all sites: • The length of the treatment or placebo balloon relative to the plain balloon has been stated to ensure appropriate application of the treatment

			• The dimensions of the treatment or placebo balloon should be determined by the largest plain balloon used in the procedure prior to the study treatment • A further fistuloplasty immediately after study treatment to treat recoil does not constitute meeting the primary endpoint The time in which the day 13 blood sample can be taken has been further defined in order to be more flexible, to account for out of office hours dialysis sessions The randomisation method has been specified as the minimisation method. We are using this method for three reasons: • Minimisation allows other radiologists at a site who don't perform the index procedure, and who will evaluate primary outcome, to be kept blinded. Using the alternative method, stratified block, where stratification would be i) by study site, and ii) whether or not the participant has had a previous intervention to the access circuit, the randomisation system would send all radiologists at a site the unblinded result. This is a limitation of the randomisation system we are using, but building a bespoke system would greatly delay the trial, thus using minimisation is appropriate. • Minimisation ensures balance between groups, avoiding confounding due to radiologists effect. • Minimisation is preferable to stratified block due to the large number of strata that result from the two stratifiers, and especially as the number of radiologists involved in the trial could change.
4.0	23 / 11 / 2015	N/A	Non-substantial amendment to the protocol including the following changes: - a change in trial statistician - re-wording in order to clarify procedures but no major change to warrant a substantial amendment.
5.0	08/03/2016	08/04/2016	Protocol changes: Eligibility Criteria (study synopsis and section 3.2; IRAS QA17-1) • Inclusion criterion 1 has been changed to include all patients who have a native AVF in the arm, regardless of whether they are on haemodialysis or not. Previously we only included those patients who have been on haemodialysis for 12 consecutive sessions. These patients represent a prevalent population that would be relevant to the study. Most participants will start dialysis during the follow-up period and so the clinical endpoints of the trial will be unaffected. Even in those participants who do not start dialysis, their fistula can be assessed clinically and therefore clinical endpoints can still be assessed. Whether the participant is on haemodialysis or not at the time of randomisation will be an additional minimisation factor (section 4.4). • The Participant Information Sheet, section 'Why have I been invited to take part?' has been

			amended to reflect this change. The PIS version referenced on the consent form has been updated as a result. Plain Balloon Fistuloplasty Procedure (section 4.3): • We have specified that an alternative high pressure balloon to the one specified can be used only if the anatomy of the lesion is such that doesn't allow the specified balloon to be used initially. We have changed this so that participants with this type of lesion are not excluded in error. Subsequent changes in section 4.5 Study Treatment relate to this specification. • For clarification, we have specified that a total of 3 plain balloon fistuloplasty treatments are allowed prior to the study treatment. Fistulograms performed for a clinical indication (section 4.7.2) • We have clarified this section to ensure that all sites clearly understand which fistulograms images are required.
6.0	07/07/2016	31/08/2016	1. Change in Project Manager (pg 2). Mrs Vikki Semik has resigned from her post and has been replaced by Dr Leanne Gardner as the Project Manager for PAVE. 2. Change in inclusion and exclusion criteria to increase participant eligibility rates. An audit of eligibility rates for PAVE indicated that a considerable proportion of patients were ineligible for the trial due to synchronous lesions in their access circuit. As there are longer drug-coated balloons (greater than 60mm) available for use in the trial, we would like to include participants with one or more lesions than can be treated with up to 120mm of a single drug-coated balloon. This will improve eligibility rates and increase recruitment to the trial without the requirement for changes analysis of trial outcomes. Inclusion criteria 6 has been altered to include participants with a treatment segment containing one or more lesions that can be treated with greater than or equal to 120mm of a single drug-coated balloon (pg 4 and 15). Exclusion criteria 4 has been altered to exclude patients with one or more lesions outside the treatment segment (pg 4 and 15). 3. Removal of details from the plain fistuloplasty procedure to increase participant eligibility rates. After consultation with a number of interventional radiologists, it was decided that if further balloon fistuloplasty treatment is required to obtain a positive result (residual stenosis is ≤ 30%), that the administration should not be restricted to two more times. Thus this paragraph was removed from the protocol (pg 17). 4. Clarification of who will be performing the measurements required for the analysis of fistulograms performed in the trial. Details indicating that it will be a core laboratory that will make the fistulogram measurements have been added to the protocol (pg 18). This was added to the protocol because the interventional radiologists were unsure as to whether or not they were required to take these measurements. 5. Details regarding the input of required information into the randomisation system have been added to the randomisation procedure section. In a previous amendment, we added that participants who were not currently on haemodialysis

			were eligible for the trial. Further detail was required in the protocol to indicate to the radiologists that this data must be entered into the randomisation system prior to randomising the participant (pg 18). 6. Clarification of the length of time participants will be on the study: Additional information has been added to the protocol to indicate that participants will remain in the study until the last patient recruited has undergone one-year of follow up. The expected duration of the trial is 3 years but it will remain open until recruitment is complete and the last recruited patient has undergone one year of follow up. 7. Clarification of procedures relating to the 6-month protocol fistulogram. We have altered the protocol to indicate that the decision to perform a protocol fistulogram, or not must be confirmed with the PI after discussion with relevant clinical colleagues (pg 19). We have also indicated that the 6-month protocol fistulogram must be performed within 6 weeks of the 6 month study assessment. This was increased from 2 to 6 weeks because additional time is required is some cases for the confirmation that a protocol fistulogram can be performed or not (pg 19). We have indicated that participants may be reimbursed for their travel expenses for attending the hospital for their 6-month protocol fistulogram. These participants will be attending the hospital specifically for this research-related procedure and not for clinical reasons. Thus we believe reimbursement for their travel expenses is justified in this case (pg 19). 8. Clarification of procedures relating to fistulograms performed for a clinical reason. In section 2.1 (page 10) we have clarified that an independent assessment of the fistulogram will be performed though this may not necessarily be a core laboratory analysis in all cases. In section 4.7.2 (p20) we have clarified that all images from fistulograms performed for a clinical indication will be sent to the lead site. Some of these (prior to 6 months) may be used for to assess angiographic secondary endpoints as stated. Some may be sent to the independent core laboratory to demonstrate a lack of bias (as stated in section 5.2). Others may be used for quality control by the lead site. 9. Collection of blood samples and clinical data from patients who have consented to the trial but are not randomised. We have added to the protocol that blood samples may continue to the taken and clinical data recorded, from consenting patients for laboratory research. These samples will be used for mechanistic studies that are planned on samples from patients who remain in the PAVE trial. Samples from patients excluded from the trial will remain useful for these studies which will examine factors in the blood pre and post fistuloplasty. The patient information sheet has also been amended to clarify this. 10. Further clarification that the intervention procedure must be performed with only a single non-drug-coated or drug coated balloon. We have added the word "single" in two sentences of the Study Treatment section (pg. 18) to ensure that the radiologists are aware that they are only to use a single non-drug-coated or drug-coated balloon for the intervention. 11. Changes to study documentation including PIS and consent form have also been made.
7.0	26/01/2017	21/03/2017	Study Synopsis: Exclusion criterion Point 4. (page 4)

			Additional detail has been added to criterion 4 to exclude patients if they have any additional lesions outside the treatment segment that are treated even if the reduction of vessel diameter of these lesions are <50%. 3.3 Exclusion Criteria Point 4. (page 4) Additional detail has been added to criterion 4 to exclude patients if they have any additional lesions outside the treatment segment that are treated even if the reduction of vessel diameter of these lesions are <50%. 3.4 Criteria for withdrawal (page 16) This section has been amended to update the criteria for withdrawal from the study. Participants will now be withdrawn from the study if their fistula is ligated, abandoned, or thrombosed and not salvageable. We no longer need to follow up these patients because the fistula that contained the treated lesion is no longer functioning and therefore does not need to be assessed. 4.1 Screening procedures (page 16) In a previous amendment (Amendment 4 08/03/2016) we were given approval to consent participants in less than 24 hours prior to the procedure providing that the patients had sufficient time to considered taking part in the trial. This would allow us to take consent on the same day as the initial procedure, which is sometime necessary. These changes were approved by the REC. However this information was not updated in the protocol. These changes have now been made to the protocol indicating that consent will be taken after the patient has had sufficient time to read the information sheet, consider the trial and ask question. 4.1 Screening procedures (page 16) All fistulograms are to be performed as digital subtraction acquisitions at 3 frames per second (fps). However at some units this is not possible. Thus we have indicated in the protocol that if equipment will not allow 3 fps then 2 fps is acceptable. The inclusion and exclusion criteria are examined at a number of different times during the screening period. Thus we have removed details when each of the criterion should be examined because most criterion are examined on a number of occasions. 4.2 The pre-procedure fistulogram (page 17) Following the pre-procedure fistulogram the radiologist will assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study. This has been clarified as some criterion need to be re-assessed following the procedure. 4.3 The plain balloon fistuloplasty procedure (page 18) Following the plain balloon fistuloplasty procedure, the radiologist will again assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study. This has been clarified as some criterion need to be re-assessed following this particular procedure. 4.6 Study assessments (page 19) For clarification purposes regarding the 6 month study assessment, details about the requirements for the 6-month protocol fistulogram have been removed from this section and added to the following section 4.7.1. 4.7.1 The 6 month protocol fistulogram (page 20)

			This section has been rewritten for clarity. It indicates that the protocol fistulogram is performed if there are no clinical concerns identified and that it can be delayed while the fistula is assessed. Following assessment and if there are no concerns the 6-month protocol fistulogram can be performed no later than 9 months after the study intervention took place. If there are clinical concerns following assessment, then the 6 month protocol fistulogram will not take place and normal clinical practice will proceed. Patients may be reimbursed for travel costs if they have their 6 month protocol fistulogram (this was previously approved by the REC). 5.1 Laboratory test (page 21) Previously, the REC had approved a reduction in the number of times a 10ml blood sample will be taken from four timepoints to three timepoints. This was updated in Table 2.3 but was not changed in the text of this section. This has now been updated. Blood samples are being taken before and after the study procedure and at the 3-month timepoint.
8.0	13/12/2017	28/02/2018	Section 2.1 Primary Endpoint: Additional information has been added to the protocol for defining the primary endpoint. This information more clearly defines the assumptions required for time to end of target lesion primary patency. Section 4.5 Study Treatment: Additional information regarding the treatment procedure and use of plain balloons and treatment balloons has been added to the protocol. This was required to more clearly describe how the procedure is carried out correctly and to limit the number of protocol deviations due to inadequate description of the procedure. The additional text is highlighted in version 8 of the protocol attached.
9.0	12/09/2018	21/12/2018	Changes to the Protocol: Contact List: (Page 1): Updated details of the Sponsor and Co-Sponsor have been added to this section. The following changes have been made to the protocol to incorporate the additional 11 month study period, and to provide clarity of information: Section 2.2 (page 11) Previous Text: We will recruit 211 patients over a two-year period. New text: We will recruit 211 patients over a three-year period. Section 2.3 Trial Schedule (page 12) Following approval of the study extension, we have increased the number of follow up assessments in the Trial Schedule to month 48. We have also updated the Trial Schedule to confirm that failure to complete the Quality of life assessments will not be deemed a protocol violation. We have also added to the Trial Schedule that blood samples may also be collected pre and 1-3 days post the protocol fistulogram at Guy's and St. Thomas' only. Section 3.1 (page 14) Previous Text: The expected accrual duration will be 22 months, and the maximum study duration

			(including followup) 34 months. New text: The expected accrual duration will be 36 months, and the maximum study duration (including follow-up) 50 months. Section 4.6 (page 19) Previous Text: It is expected that the study will remain open for 3 years. New text: It is expected that the study will remain open for 4 years. Section 5.1 (page 21) For clarity, the second paragraph of this section has been updated to say Trial Schedule rather than table of events. Previous Text: Blood (up to 90 ml) may be taken at each of the time points in the table of events in 2.3. New text: Blood (up to 90 ml) may be taken at each of the time points in the Trial Schedule in 2.3.