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Anaesthesia Choice for Creation of Arteriovenous Fistulae ACCESs

STATISTICAL ANALYSIS PLAN (SAP)

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1. INTRODUCTION

1.1. STUDY BACKGROUND

Arteriovenous fistulae (AVF) are the "gold standard" vascular access for haemodialysis, however universal usage is limited by a high early failure rate. Several small studies, including our own single-centre randomised controlled trial (RCT), previously demonstrated better early patency rates for AVF created under regional anaesthesia (RA) versus local anaesthesia (LA). The mechanistic hypothesis is that sympathetic blockade causes vasodilatation and increased blood flow through the new AVF. Despite this, considerable variation in practice exists in the UK. A high quality, adequately powered, multicentre RCT is required to definitively inform practice and that is the purpose of this study.

1.2. STUDY OBJECTIVES

The primary objective of the study is to compare unassisted functional AVF patency at 1 year in patients undergoing primary creation of radiocephalic fistula (RCF)/brachiocephalic fistula (BCF) under RA versus LA.

The secondary objectives of the study are:

1. To compare the efficacy (quality of anaesthesia) provided by LA and RA in patients undergoing primary RCF/BCF creation
2. To compare the safety of LA and RA in patients undergoing primary RCF/BCF creation
3. To compare the acceptability of LA and RA in patients undergoing primary RCF/BCF creation
4. To compare rates of re-intervention, access-related complications, hospitalisations and need for alternative access in patients undergoing primary RCF/BCF creation under RA and LA
5. To compare mortality in patients undergoing primary RCF/BCF creation under RA and LA
6. To compare dialysis and access modality utilised in patients undergoing primary RCF/BCF creation under RA and LA
7. To evaluate the cost-effectiveness of RA versus LA for primary RCF/BCF creation

1.3. STUDY DESIGN

A multicentre observer-blinded, parallel group, RCT with internal pilot and embedded process evaluation study.

1.4. RANDOMISATION

An interactive web response system (IWRS) will randomise patients 1:1 to the intervention group (RA) and comparator group (LA). Permuted blocks will be used stratified by centre, dialysis status (pre-dialysis/haemodialysis) and site of AVF (RCF/BCF).

1.5. Sample Size and Power

Section 10.1 of the study protocol states:

> *"566 subjects (283 per arm) will be required to detect a 15% difference in the primary outcome measure with 5% significance level and 90% power, assuming that 15% of subjects will be lost to follow-up, will change RRT modality or die."*

1.6. Statistical Analysis Plan (SAP)

1.6.1. SAP Objectives

The objective of this SAP is to describe the analyses to be carried out for the ACCESs final analysis.

The current version of the protocol at the time of writing is version 2.1 dated 09/02/2023. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. This will be documented as part of the Robertson Centre Impact Assessment process.

1.6.2. General Principles

Data will be summarised overall and by treatment group. Continuous variables will be summarised using the number of observations, number missing, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3 respectively), minimum and maximum values.

Categorical variables will be summarised with the number of observations, number missing and the number and percentages of participants falling into each category.

1.6.3. Deviations To Those Specified In Study Protocol

The analyses described in this SAP are consistent with the current protocol.

1.6.4. Additional Analyses To Those Specified In Study Protocol

There are no planned additional analyses to those described in the current protocol.

1.6.5. Software

Analyses will be conducted using SAS for Windows v9.4, or higher, and R version 4.3.0 or higher.

2. Analysis

2.1. Study Populations

The randomised population will include all randomised patients.

The Full Analysis Set (FAS) will consist of all subjects in the randomised population that were not randomised in error, i.e. excluding any participants who were found, post-randomisation, to have not met the entry criteria. The list of participants to be excluded will be agreed prior to database lock. The FAS will be considered the principal analysis set for the primary and secondary outcomes and for the exploratory efficacy outcomes. Following the ITT principle, patients will be analysed according to their randomised group, irrespective of the treatment received, their protocol adherence, and their continued participation in the study.

The Per Protocol population will consist of all members of the FAS, excluding those with major protocol deviations. Major protocol deviations will be identified from eCRF data, plus any deviations reported during the study. All reported protocol deviations will be reviewed prior to database lock and classified as major and minor in relation to the SAP. Major protocol deviations will include not getting surgery as intended as indicated by confirmation of surgery, receiving the wrong treatment according to the randomisation, and not being followed up as per protocol. Additional analyses of the primary outcome may be carried out using this population after the initial ITT analyses of the FAS.

The Safety Set (SS) will consist of all randomised participants who received either local or regional anaesthesia. The SS will be used for all safety analyses. Safety analyses will be conducted in relation to the treatment received.

2.2. STUDY STATUS

The flow of patients in the study will be described according to CONSORT guidelines, with the number and percentage of subjects presented and summarised for the regional anaesthesia (RA) and local anaesthesia (LA) groups separately:

- Consented
- Meeting eligibility criteria
- Randomised
- Attended each visit
- Withdrawn consent (and reasons where available)
- Not undergone surgery (and reasons where available)
- Received allocated treatment
- Randomised population, FAS, and SS membership

Note that screening data is maintained locally at sites and this information will also be used when producing the CONSORT diagram to determine the number of people approached.

2.3. PROTOCOL DEVIATIONS

At the end of the study, a list of protocol deviations will be provided and these will be classified as major or minor. Major and minor classification of deviations will be agreed with the CI and trial statistician, and documented as part of the lock process. All major protocol deviators will be excluded from the FAS for the analyses.

Visits that take place outwith the study visit window will be classed as minor protocol deviations and will not be excluded from the FAS. Summaries of the time since baseline to the study visits will be included.

2.4. BASELINE CHARACTERISTICS

The following baseline characteristics and measures will be summarised overall and by randomised group for both the randomised population and the FAS, without formal statistical comparison:

- Demographics: age, gender, ethnicity, dialysis status, site of arteriovenous fistula (AVF), body mass index
- Medical history: diabetes, hypertension, ischaemic heart disease, cerebrovascular accident, primary renal disease
- Concomitant medications: aspirin, clopidogrel, warfarin, other antiplatelet, other anticoagulant
- Vital signs: systolic and diastolic blood pressure, heart rate
- AVF planning: current renal replacement therapy modality, eGFR (where applicable), previous AVF details, ultrasound findings including artery and vein diameters

2.5. EFFICACY OUTCOMES

2.5.1. PRIMARY OUTCOME

In order to compare unassisted functional AVF patency at 1 year in patients undergoing primary RCF/BCF creation, unassisted functional patency will be defined as the ability of an access to uninterruptedly deliver the prescribed dialysis without intervention. In pre-dialysis patients this will be assessed clinically and ultrasonographically (4mm diameter and access flow >500ml/min). If a subject has not had an ultrasound and has no response for the ultrasound criteria for unassisted patency, the fistula is deemed patent by clinical assessment only. The number of subjects that meet both of the conditions (ultrasound and clinical assessment) and also the number that only meet one of the criteria will be reported overall and by randomised treatment group, alongside the number of subjects where the fistula has a bruit. Unassisted functional patency will also be reported split by dialysis status.

Unassisted functional patency will be analysed using a logistic regression model. The model will adjust for the randomisation stratification variables (dialysis status and site of AVF), age, diabetes, gender, ethnicity, and randomised treatment group with a random effect for centre included in the model. The odds ratio (OR), 95% confidence interval and p-value will be presented for the outcome.

2.5.2. SECONDARY OUTCOMES

The secondary outcomes relating to each of the objectives are:

1. Compare efficacy provided by LA and RA in subjects undergoing AVF creation

    a) Pain score at incision, at 30 minutes and 1 hour postoperatively

b) Speed of onset/quality of motor and sensory block
c) Need for anaesthetic supplementation/"failed block"
d) Volume of anaesthetic agent
e) Time taken to administer anaesthetic

Outcome 1a will be summarised at each time point by randomised treatment group. Linear regression models will be used to compare the pain scores at each time point between the treatment groups, adjusting for the randomisation stratification variables and randomised treatment group.

Outcome 1b will be assessed in the RA group at two time points, 15 and 30 minutes, with motor and sensory blocks analysed separately. Each of the nerves will summarised separately for both motor and sensory blocks. The score for each nerve will be used to determine if there is no block (score of 0 for each of the nerves), complete block (score of 2 for all nerves), or partial block (where all of the scores are not all 0 or not all 2) for both the motor and sensory blocks separately. The number and percentage of subjects in the RA group with no block, complete or partial block at these time points will be summarised.

Outcome 1c will be summarised by randomised treatment group. A "failed block" is defined as the need to convert to general anaesthesia or abandonment of surgery. A logistic regression model will also be used to analyse this outcome, adjusting for the randomisation stratification variables (dialysis status and site of AVF), age, gender, diabetes, BMI, ethnicity, arterial and venous diameter at site of AVF creation, and randomised treatment group. A random effect for centre will also be included in this model. The estimated odds ratio, 95% confidence interval and p-value will be presented. Conversion to general anaesthesia and abandonment or surgery will also be summarised separately by treatment group, and logistic regression models may be used to analyse these separately. It will also be of interest to summarise the number of subjects requiring supplementation or additional sedation by treatment group.

Outcomes 1d and 1e are not specifically related to block efficacy. The volume of anaesthetic used during the surgery will be summarised overall and by treatment group. This will be summarised as the initial dose administered and then a separate summary for the total volume administered including any supplementation. Statistical comparisons will be carried out to determine if there is a difference between the two treatment groups. The time taken to administer anaesthetic will be reported in the RA group and this is taken as the time from the probe being placed on the skin to the time the block was completed.

The total time from start of anaesthesia to start of surgery will be reported overall and by treatment group. In the RA group, this is the time between the probe being put onto skin and the knife being put onto the skin. In the LA group, this is the time between the local anaesthetic being injected and the knife being put onto skin.

2. Compare the safety of LA and RA in subjects undergoing AVF creation

    a) Adverse events relating to anaesthesia e.g. pneumothorax, intravascular injection, systemic toxicity
    b) Technical difficulties delivering anaesthesia e.g. inability to identify structures, misplacement, paraesthesia

    Summaries will be produced looking at each of the above safety outcomes by randomised treatment group.

3. Compare acceptability of LA and RA in subjects undergoing AVF creation

    a) Patient satisfaction scores

    The patient satisfaction with anaesthetic technique will be summarised for each randomised treatment group. To compare the patient satisfaction between the treatment groups, a linear regression model will be used adjusting for randomisation stratification variables (dialysis status and site of AVF), randomised treatment group, age, diabetes, gender, ethnicity with a random effect for centre included in the model also. The treatment effect, 95% confidence interval and p-value will be presented.

4. Compare rate of re-intervention, access-related complications and need for alternative access in subjects undergoing AVF creation under LA and RA

    a) Access complications (including infection, stenosis, thrombosis, steal, bleeding)
    b) Re-operation/re-intervention to maintain or re-establish patency (revisional surgery, angioplasty, stenting or thrombectomy)
    c) Alternative accesses e.g. CVCs
    d) Access-related hospitalisation

    The number of subjects who experience each of the access complications listed above will be summarised by randomised treatment group. Each type of re-operation/re-intervention, the number of subjects who undergo each of these will also be summarised by randomised treatment group.

    Time-to-event analyses will be carried out using Kaplan Meier plots to visualise the difference in time to event for outcomes 4a and 4b above and log-rank tests will be used and p-values will be presented to test the difference between the treatment groups.

    For outcome 4c, the total number of alternative accesses and the number of different types of alternative access will be summarised overall and by treatment group. Any intervention required for alternative access and the number of interventions required will be summarised.

    The number of access-related hospitalisations will be summarised overall and by randomised treatment group.

In addition to the above, the time to loss of a) primary patency and b) primary assisted patency, and c) secondary patency will also be assessed. Each of these outcomes will be determined from the date of creation of the fistula. Time to first loss of primary patency is defined as the time to first thrombosis or first intervention to maintain/re-establish patency. Time to first loss of primary assisted patency is defined as the time to first thrombosis (regardless of whether the fistula was successfully salvaged). The time to first secondary patency is defined as time to first loss of thrombosis when the fistula could not be salvaged. Each outcome, will be analysed by carrying out a time-to-event analysis using a cox proportional hazards model. Randomised treatment group, age, diabetes, gender, ethnicity, and randomisation stratification variables (dialysis status and site of AVF) will be included in the model as covariates with a random effect for centre included in the model also. The estimated treatment effect, 95% confidence interval and p-value will be presented for each model.

5. Compare mortality in patients undergoing AVF creation under LA and RA

    a) Mortality (date and cause)

    The number of deaths and the cause of death will be summarised by randomised treatment group. Time to death will be analysed carried out using Kaplan Meier plots to visualise the difference in time to event for each outcome and log-rank tests will be used and p-values will be presented to test the difference between the treatment groups. The number of deaths within 30 and 90 days will also be reported by treatment group.

6. Compare dialysis and access modality utilised in subjects undergoing AVF creation under RA and LA

    a) Time from randomisation to commencement of HD
    b) Access modality at start HD
    c) Change of RRT modality
    d) Change of access modality

    Summaries will be produced looking at each of the above outcomes by randomised treatment group, including the number and percentage of subjects on HD at 12 months. Summary data will be presented at 0, 3 and 12 months to show the RRT modality at each time point and similarly, access modality at the start of haemodialysis and any changes in access modality will be summarised.

7. Evaluate cost-effectiveness of RA versus LA for AVF creation

    a) EQ-5D-5L
    b) KDQOL-SF
    c) VASQOL

    All outcomes for objective 7 will be summarised by randomised treatment group at all study visits where the data is collected.

For the VASQOL questionnaire, if a subject has multiple accesses and therefore completes the VASQOL more than once, for each question, the worst score across all accesses will be used. When summarising the VASQOL, the satisfaction and impact domain scores as well as the total domain score will be summarised overall and by treatment group.

2.5.3. SUB-GROUP ANALYSES

All subgroup analyses will be provided for the primary outcome (unassisted functional patency).

For each level of response within each subgroup, the number and percentage of subjects that have unassisted functional patency at 1 year will be reported, split by treatment group. The odds ratios, 95% confidence intervals and p-values for the treatment effects comparing the two treatment groups will be provided within each subgroup group using logistic regression. The primary outcome model will be extended to include the subgroup variable and the interaction between the subgroup and the treatment effect with a p-value for the interaction calculated.

The subgroups that will be examined are:

- Dialysis status (pre-dialysis/haemodialysis)
- Site of AVF (RCF/BCF)
- Age (<65 / >= 65 years old)
- Gender (male/female)
- Diabetes (yes/no)

2.5.4. ADDITIONAL ANALYSES

Below are some additional analyses that will be conducted in addition to the protocol-specified analyses.

- Duration of the surgery will be summarised overall and by randomised treatment group. This is the time between knife to skin and the surgery being completed. An appropriate statistical test (t-test or Wilcoxon test) will be conducted to determine if there is difference in the duration between the two randomised treatment groups. Mean difference in the outcome will be presented, with the 95% confidence interval and p-value.

- The total supplemented volume will be summarised for each randomised treatment group. In the RA group, the volume for the supplemented block and the volume of local anaesthesia supplementation will be summarised separately.

- Additional details of the surgery and anaesthesia will be summarised by the number and percentage of subjects in the RA group. These include:

    - Axillary vs supraclavicular
    - Complications of block including paraesthesia and aspiration of blood

- Structures identified whilst block was performed: Musculocutaneous nerve, median nerve, ulnar nerve, radial nerve and medial cutaneous nerves

2.5.5. Sensitivity Analyses

After the initial analysis of the FAS population according to the ITT principle, additional sensitivity analyses may also be carried out excluding those randomised subjects that had a "failed block".

It may also be of interest to carry out a sensitivity analysis removing those randomised subjects where the anticipated site of surgery differs from the actual site of surgery.

A further sensitivity analysis may be conducted for the primary outcome where surgeon within centre is included in the primary analysis model as a nested random effect.

2.5.6. Assumption Checking

The proportional hazards assumption will be checked when fitting the Cox Proportional Hazards models. This will be done both graphically using Kaplan-Meier plots, and formally by adding a log(time)*treatment covariate to the relevant models and assessing the statistical significance.

2.6. Safety Outcomes

2.6.1. Premature Withdrawal

The number of subjects that withdraw from the study and their reason for withdrawal will be summarised in the subject disposition summaries.

2.6.2. Adverse Events and Serious Adverse Events

The number and characteristics of adverse events (AE) and serious adverse events (SAE) will be summarised as a whole and by randomised treatment group where treatment received is known. The number and percentage of subjects experiencing at least one AE/SAE will be summarised overall and by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

SAEs that are related to the vascular access will be summarised separately for the whole population and by randomised treatment group. During the CI review of SAEs, each event related to the vascular access has been flagged in the data and can be used to pull out relevant events for these summaries.

3. Data Conventions

A separate assumptions document will be created detailing data rules (e.g. partial dates, missing data imputation).

4. TABLES AND FIGURES

Dummy tables and figures will be produced during the development of the statistical analysis programs for review and feedback. Approval of the content of the final statistical outputs will be a requirement for database lock.

5. DOCUMENT HISTORY

This is version 1.2 of the ACCESs final analysis SAP, dated 17/10/2024. V1.1 of the SAP was updated to:

1. Update the definitions of the study populations
2. Specify the vessel diameters being used as part of the analysis for secondary outcome 1c.