Statistical Analysis Plan (SAP)

For the extension of

"A randomized clinical trial to compare early versus delayed endovenous treatment of superficial venous reflux in patients with chronic venous ulceration – EVRA"

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1 Approval Signatures

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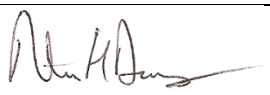
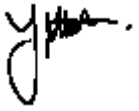
Prof Alun H Davies		Chief Investigator	22/08/19
Prof Julie Brittenden		TSC Chair	22/08/19
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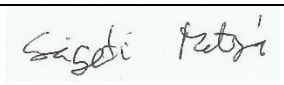
Matyas Szigeti		Trial Statistician	22/08/19

2 Introduction

Chronic leg ulcers are open "sores" on the lower limbs situated between the ankles and knees, which fail to heal within 6 weeks. The underlying cause of leg ulceration in over 70% of cases is lower limb venous dysfunction, sometimes evident as varicose veins but often undetectable by visual examination alone. The estimated overall prevalence of active venous ulceration is as high as 1.5 to 1.8 per 1000 population, increasing to 3.8 per 1000 population in those over 40 years of age. As patients with venous ulceration usually suffer episodes of recurrence between periods when the ulcer remains healed, the number of patients with a high risk of ulceration may actually be 4-5 fold higher.

Venous ulcers are characterised by protracted healing times and frequent recurrences. Despite some recent advances in the management of patients with venous ulcers, 24 week healing rates in published randomized trials are around 60-65%, and the true population healing rates are likely to be significantly lower.

For over a century, the treatment of superficial venous reflux has involved operative ligation and surgical stripping of the vein and avulsion of bulging varicose veins. Until recent years, open surgery has been considered the definitive treatment option for superficial venous reflux. However, the operation usually requires general anaesthesia and patients often suffer discomfort, bruising and significant time off work in the post-operative period. In addition, long-term studies have also identified significant complications of open surgery. In response to this high complication rate and a growing patient desire for less invasive treatments, a range of novel, minimally invasive endovenous treatment options have been developed and have gained in popularity over the last decade. Non-randomized studies suggest that outcomes may be improved by treating underlying superficial reflux using the latest technologies. The EVRA study was the first randomised trial to demonstrate improved healing outcomes after early intervention. An understanding of medium and long-term outcomes will allow greater appreciation of the impact of early endovenous intervention beyond the first year.

2.1 Study Objectives

2.1.1 Primary Objective

To study the long term effectiveness of early endovenous treatment of superficial venous reflux in addition to standard care compared to standard care alone in patients with chronic venous ulceration.

2.2 Study Population

Patients with leg ulceration referred to secondary care as part of the standard care pathway.

2.3 Study Design

The EVRA ulcer trial is a pragmatic, multicentre randomized clinical trial with participants randomized 1:1 to either:

'Standard' therapy consisting of multilayer elastic compression bandaging / stockings with deferred treatment of superficial reflux (usually once the ulcer has healed)

Early endovenous treatment of superficial venous reflux (within 2 weeks) in addition to standard therapy

With the study extension, the duration of follow-up is up to 5 years (median follow-up approximately 3.7 years).

2.4 Data collection during the extension period

For each randomised patient a single telephone assessment will be performed between 1st October 2018 and 31st March 2019 to collect:

• Details of any further ulcer recurrence and healing events

• Assessment of ulcer related healthcare attendances and costs

• Details of all further venous interventions performed and any associated adverse events

• Assessments of disease specific and generic quality of life (AVVQ, EQ5D & SF36) by means of self-completed questionnaire completed over the telephone (or via post)

2.5 Long term outcomes

All outcomes will be evaluated using data from the entire study (main study and extended follow-up period) unless stated otherwise.

2.5.1 Primary outcome

The primary outcome measure will be time to first ulcer recurrence on the randomised leg from date of healing. For the purposes of this study, ulcer healing is defined as complete re-epithelialisation of all ulceration on the randomised (reference) leg in the absence of a scab (eschar) with no dressing required.

2.5.2 Secondary outcomes

1. Time to the first ulcer recurrence on the randomised leg from the date of randomisation.
2. Ulcer recurrence rate
3. Time to healing of initial (index) ulcer
4. Ulcer free time
5. Time to healing of recurrent ulcers
6. Compliance with compression bandaging
7. Quality of life (AVVQ, EQ5D & SF36)
8. Cost-effectiveness/health economic analysis

2.6 Study Sample Size

Assuming that 90% of EVRA participants experience ulcer healing and 15% withdraw or are lost to follow up, 344 participants will be available for the analysis of long-term outcomes (450 x 0.9 x 0.85). All patients that have not withdrawn from the study or died will be followed-up. The ulcer recurrence rate is expected to be 38%, based on evidence from the ESCHAR trial and it is known that approximately 95% of participants in the early arm and 85% in the delayed arm experienced ulcer healing by 12 months. With 344 participants (182 in the early arm and 162 in the delayed arm), the study will have 82% power to detect an absolute difference in recurrence rate of 15% (30% early arm vs 45% delayed arm) and 97% power to detect an absolute difference in recurrence rate of 20% (30% early arm vs 50% delayed arm).

2.7 Randomisation

Not applicable

2.8 Schedule of Time

Data collection for the long-term follow-up will be between 1st October 2018 and 31st March 2019.

3 General Considerations

3.1 Analysis Strategy

All analyses will be on an intention-to-treat basis unless specified otherwise. Histograms and boxplots will be used to check the distribution and possible outliers for continuous variables. Mathematical transformations might be applied, where appropriate, in order to render the continuous variables' distribution normally distributed. Continuous variables that follow an approximately normal distribution will be summarised using means and standard deviations. Skewed continuous variables will be summarised using medians and inter-quartile ranges. Categorical variables will be summarised using frequencies and percentages.

For the primary outcome (time to the first recurrence), the hypothesis that there is no difference between the control and intervention groups will be tested using a Cox model (with study centre grouped by region as a random effect). The primary result will be adjusted for age, ulcer size and ulcer chronicity. Kaplan-Meier survival curves for each treatment group will also be presented. The time to the first recurrence is defined from the date of ulcer healing to the date of first recurrence.

Time to ulcer healing will also be assessed using a Cox model with centre as random effect and adjusted for age, ulcer size and ulcer chronicity. Kaplan-Meier curves for each treatment group will also be presented.

Ulcer recurrence rate will be obtained from the Kaplan-Meier analysis of the primary outcome and the rates in each arm will be calculated at annual time points with associated 95% confidence intervals.

Ulcer free time will be analysed using survival analysis (to account for censoring) and median ulcer free time, with associated 95% confidence intervals, will be presented for each group.

The difference in ulcer free time between the treatment groups will be assessed using Cox regression adjusted for the same factors as the primary outcome.

Time to healing of the recurrent ulcer (from date of recurrence to date of healing) will be assessed as for the primary outcome using Cox model with centre and patient as random effect. Kaplan-Meier curves will be used to present the data.

Compliance will be compared between the two arms and possible relationships and patterns between subgroups and other recorded factors that might influence compliance will be explored.

Quality of life measurements will be compared between arms using 3-level mixed models and will be summarised for each timepoint.

Health economic assessment will be carried by the trial health economist and thus will not be included in this statistical analysis plan (See Extension Health Economic Analysis Plan).

3.2 Definition of Population for Analysis

Analysis of the primary outcome will be on an “intention to treat” (ITT) basis and will include all participants who were randomised in their allocated groups. Participants whose first ulcer has not healed are not at risk of recurrence and so will effectively be excluded (as they will drop out from the numbers at risk). Analysis of the secondary outcomes will also be on intention to treat with all randomised participants included where possible. For time to recurrence from date of healing, participants whose first ulcer has not healed will be excluded. For time to healing of recurrent ulcer, participants without ulcer recurrence will be excluded. A secondary per-protocol analysis of time to healing and time to first recurrence (from healing) will also be carried out by excluding patients with the following protocol deviations:

1) Patients randomised to multilayer compression / stockings plus early venous reflux ablation, who receive endovenous intervention more than two weeks from randomization.

2) Patients who are non-compliant with compression bandaging, defined as use <75% of the prescribed duration.

3) Patients randomised to compression bandaging alone who undergo endovenous ablation prior to verified healing.

3.3 Data Management

Data is collected and managed using InForm: an electronic data capture system built around an Oracle database. The InForm system includes validation rules for data entry to help ensure data accuracy, and has a full audit trial of data entry and changes. Data queries will be raised for inconsistent, impossible or missing data.

3.4 Missing Data

There will be no data imputation for missing data in any outcome. However, the level and pattern of the missing data in the baseline variables and outcomes will be reported. The potential causes of any missingness will be investigated and documented as far as possible. Any missing data will be dealt with using methods appropriate to the conjectured missingness mechanism and level of missingness.

3.5 Level of Significance

The primary outcome and secondary outcomes will be tested using a two-tailed hypothesis test with a 5% significance level. For secondary outcomes, there will be no adjustment for multiple testing.

3.6 Losses to Follow-up and Withdrawals

All the primary analyses will be performed on an intention-to-treat basis. Only patients willing to undergo either immediate or delayed superficial venous ablation with compression bandaging are randomised. Subjects who die, withdraw from the study, or are lost to follow-up before ulcer healing will be censored in the Kaplan Meier and Cox regression analyses at last follow-up visit.

3.7 Deviations from the SAP

All deviations from the SAP will be disclosed in the final analysis report. If problems or fundamental issues become apparent in the on-going checking that forms part of the statistical analysis, the trial statistician will raise these with a senior statistician who will consult with the appropriate individuals. Any such action and subsequent decisions will be documented in the final statistical analysis report.

4 Analysis Plan

4.1 Recruitment Details

Details about patient enrolment, follow-up and inclusion in analysis will be provided using a consort diagram. This means that the main phase's consort diagram will be extended with the extensions follow up data.

4.2 Baseline Characteristics

Baseline characteristics would be the same as in the main phase and therefore will not be presented. Instead, a CONSORT diagram will summarise the follow up details and the reasons for drop out.

4.3 Time to ulcer recurrence

The primary outcome is time to the first recurrence from the time first ulcer was healed. We will test the hypothesis that there is no difference in this between the control and intervention groups using a Cox model with study centre as a random effect. Kaplan-Meier survival curves and the log-rank test result will also be presented. Both unadjusted and adjusted (age, ulcer chronicity, ulcer size. Hazard Ratios (HR) and their 95% Confidence Interval (CI) will be presented but the adjusted results will be taken as primary. For Cox regression models the proportionality assumption will be assessed graphically (using diagnostic plots). A secondary analysis will be undertaken as above but with time to ulcer recurrence measured from time of randomisation rather than time of healing. As a sensitivity analysis, the above will be repeated in the per-protocol population.

4.4 Time to ulcer healing

Time to ulcer healing is defined as the time from the date of randomisation to the first ulcer healing on the randomised leg. Similarly to the primary outcome we will test the hypothesis that there is no difference in this between the control and intervention groups using a unadjusted and adjusted Cox model with study centre as a random effect. Adjusted results will be taken as primary and the adjustment factors will be age, ulcer chronicity, ulcer size. Kaplan-Meier survival curves and the log-rank test result and HR with 95% CI will be also presented. As a sensitivity analysis, the above will be repeated in the per-protocol populations.

4.5 Ulcer recurrence rate

Ulcer recurrence rate defined as the proportion of patients who had an ulcer recurrence at a defined timepoint. This will be obtained from the Kaplan-Meier analysis of the primary outcome and the rates in each arm will be calculated for annual time points with associated 95% confidence intervals.

4.6 Ulcer free time

Ulcer free time is defined as the time between randomisation and the end of follow-up when the randomised leg was free of ulcer. The preferred method of analysis is to use Cox regression to assess the difference between the treatment arms, with centre as a random effect, unadjusted and with adjustment for follow-up time, age, ulcer size and ulcer chronicity. The adjusted results will be taken as primary. In the case that a patient is dead, withdrawn or lost to follow-up, ulcer free time will be calculated as the time from randomisation until last follow-up. Graphical methods will be used to assess whether the assumptions are met. If the assumptions are not met, and there is no suitable

transformation, ulcer free time will be compared by ordinal regression or negative binomial regression or multiple events survival modelling. Model fit will be assessed using residual plots and/or goodness-of-fit tests, as appropriate.

4.7 Healing of recurrent ulcer

Healing of a recurrent ulcer (any) is defined as the time between the date of the recurrence and the date of the healing of the recurrent ulcer. This could happen multiple times per patient and all of the recurrent ulcers will be included the analysis. To test for a difference between the treatment groups, healing time of recurrent ulcers will be analysed using three level Cox regression, if possible, with study centre and patient as random effects. Should the fitting of a three level model not be possible (through lack of convergence, for example), a two level model (with patient only as a random effect) will be used instead with study centre included as a fixed effect. This will be also adjusted for age, ulcer size and ulcer chronicity. Kaplan-Meier survival curves and the log-rank test result and HR with 95% CI will be also presented.

4.8 Compliance with compression bandaging

Compliance will be compared between the two arms and possible relationships and patterns between subgroups and other recorded factors that might influence compliance will be explored.

4.9 Quality of life

The quality of life questionnaires include disease specific (AVVQ) and generic (EQ5D & SF-36) components. AVVQ will be recoded according to its manual. The SF-36 will be scored

using Health Outcome Scoring Software 5.1 for the physical health and mental health dimensions, and all eight scales, including physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.

The QoL scores will be presented using line plots for each study arm to illustrate trends in AVVQ score, SF-36 and EQ-5D-5L over time. Depending on the distribution of the data, the means and SD or medians and inter-quartile ranges at baseline, 6-weeks, 6-months and 12-months after randomisation and at the end of follow up, will be reported. 3 level mixed models be used to explore changes in QoL over time and assess the difference between the two intervention groups using grouped centre and patient as random effect.

4.10 Safety data analysis

Adverse events will be summarised by the following tables:

- number of adverse events and the number of subjects who have adverse events by category and treatment group;
- number of adverse events by category and relationship to study treatment;
- number of adverse events reported for individual subjects by treatment group.

In addition, the following listings will be produced:

- All serious adverse events