Imperial College London

ICTU
Imperial Clinical Trials Unit

# Statistical Analysis Plan (SAP)

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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EVRA

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Prepared by Xinxue Liu (Trial Statistician) with contributions from Jane Warwick

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## Approvals

This SAP is approved by:

| Version | Name | Role | Signature | Date |
|---|---|---|---|---|
| 4.0 | Professor Alun H Davies | Chief Investigator | | 9/11/2017 |
| | Dr Jane Warwick | Senior Statistician | | 9/11/2017. |
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| | TSC committee | | | 09/11/2017. |

## Contents

## 1. 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. 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, but there is no robust evidence to support early intervention. Therefore, we believe that there is a cogent argument for conducting this trial at this time.

### 1.1 Study Objectives

***Primary Objective***

To study the clinical and cost 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.

***Secondary Objectives***

- To assess the ulcer free time to 1 year
- To assess the technical success of endovenous interventions

### 1.2 Study Population

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

### 1.3 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

### 1.4 Study Outcomes

***Primary Outcome***

The primary outcome measure will be time to ulcer healing (from date of randomization to 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.

***Secondary Outcomes***

- Ulcer Healing Rate: 24-week healing rate will be reported in addition to time to ulcer healing.
- Ulcer reoccurrence / Ulcer Free Time: Will be calculated up to 1 year for each study arm.
- Quality Of Life (QoL): Disease specific (AVVQ) and generic (EQ5D & SF36) quality of life assessments will be compared at 6 weeks post randomisation, 6 months and 12 months.
- Health Economic Assessment
- Other Markers of Clinical Success: The Venous Clinical Severity Score (VCSS) and will be assessed at 6 weeks. In addition, the incidence of complications related to the endovenous intervention as well as the presence of residual / recurrent varicose veins will also be assessed at 6 weeks.

### 1.5 Study Sample Size

The sample size calculation for this study was based on the primary outcome of ulcer healing. According to previous published literature, the 24-week healing rate in patients randomised to standard treatment (compression alone) was approximately 60%, while the 24-week healing rate of early treatment of superficial venous reflux may be as high as 82%[1,2].

In order to calculate a sample size for this study, we estimate a benefit associated with early treatment of around 15%. To identify a difference in 24-week healing rates of 15% between the two groups (60% vs 75%) with 90% power and allowing for 10% dropout, the study will therefore require 416 subjects (208 per group).

### 1.6 Randomisation

The normal clinical team will make initial contact with potentially eligible patients at the referral visit.

Those who consent will be registered on the InForm ITM (Integrated Trial Management) System, a web-based data entry system, which is maintained by ICTU, and their eligibility for the study confirmed. A randomization list will be loaded onto the InForm system for each centre (as stratification will be by centre) before recruitment commences, having been prepared

in advance by a statistician who is independent of the study. Each potential participant, if confirmed to be eligible, will be assigned the next available entry in the appropriate randomization list (i.e. without foreknowledge). Thereafter, treatment allocation will not be blinded (with the exception of assessment of ulcer healing). For patients with bilateral venous ulceration, the worst leg (according to the patient) will be designated the 'reference leg'. Interventions may be performed on both legs, if deemed appropriate by the responsible clinician.

### 1.7 Schedule of Time

The study started on 24th October 2013 and is expected to recruit for about two years and follow up for another year after the recruitment of last patient. The overall study timetable is summarised in Figure 1. The independent Data Monitoring Committee (DMC) meeting will be scheduled yearly with a Chairman's review every 6 months.

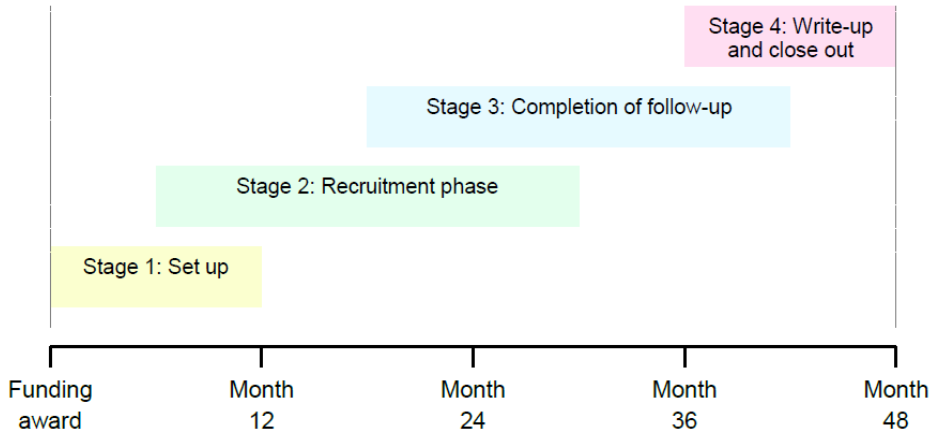


Figure 1 EVRA study Gantt chart

## 2. General Considerations

### 2.1 Analysis Strategy

All the primary analyses will be on an intention-to-treat basis. Histograms and boxplots will be used to check the distribution and possible outliers for continuous variables. Mathematical transformations will 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.

The primary outcome is time to complete healing and 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 will also be presented. As a subsidiary analysis we will investigate the effect of potential confounders (age, ulcer chronicity and ulcer size) on the treatment effect and time to complete healing using Cox regression, again with centre included in the Cox regression analysis as random effect (Table 9).

For the secondary outcome of ulcer free time, multiple regression (ordinal, if not normally distributed) will be used to adjust for the above covariates.

The quality of life (QoL) data will be summarised across baseline, 6-week, 6-month and 12-month after randomisation for both arms by means and 95% confidence intervals (CI) or median and inter quartiles, depending on the distribution of the data.

Health economic assessment will be carried by the trial health economist and thus will not be included in this statistical analysis plan.

### 2.2 Definition of Population for Analysis

The study population will comprise all participants who were randomised. A secondary per-protocol analysis will also be carried out after excluding patients with protocol violations. For the analysis of ulcer free time, the population for analysis will be patients with complete follow-up data only. This is because ulcer free time to one year depends on the time of primary ulcer healing and duration of recurrent ulcer (for example, patients with ulcer free time of 0 day may have an unhealed primary ulcer at 1 year follow-up, or may have withdrawn from the study after healing at month 1, or may have withdrawn from the study after healing at month 11). By adding this constraint some bias may have been introduced (as the analysis will have been based on complete cases only) but ulcer free time will have only one interpretation. As a

sensitivity analysis, the analysis of ulcer free time will therefore be repeated using all the patients, irrespective of length of follow up. This should give a very conservative estimate of the treatment effect.

### 2.3 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.

### 2.4 Missing Data

There will be no data imputation for missing data in the primary endpoint (time to healing) and the secondary endpoints of 24-week healing rate and ulcer free time. 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.

### 2.5 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.

### 2.6 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. All randomised participants will be followed-up for one year (irrespective of whether or not they underwent allocated treatment). For those participants unable or unwilling to attend follow-up appointments, home-visits or follow-up by community nurses may be considered.

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.

### 2.7 Protocol Violations

A high rate of protocol violations was seen in previous trials of venous ulceration (including the ESCHAR trial) and this is likely to reflect the reluctance and apprehension of elderly patients to undergo surgical interventions involving general anaesthesia. The treatment of superficial venous disease involves a range of minimally invasive, endovenous modalities that can be performed using local or no anaesthesia. Procedures are performed on an outpatient basis and can be completed in around 30 minutes. Published studies of endovenous interventions have demonstrated excellent patient satisfaction and few treatment refusals. Due to the published evidence and extensive personal experience among the research team, we believe that the rate of participation will be higher and rate of protocol violations will be lower than previous studies.

The following will be recorded as 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.

The type and reason of protocol violation will be documented in this study, and the summary of protocol violations will be reported in both arms.

### 2.8 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.

## 3. Interim Analysis

No formal interim analyses are planned. Informal interim analyses will be performed if requested by the Data Monitoring Committee (DMC) but findings will be made available to members of the DMC only. Unless advised by the DMC in response to clear evidence of benefit or hazard, the Steering Committee, collaborators, participants and all study staff (except those who provide the confidential analyses to the DMC) will remain blind to the results until the end of the study.

## 4. Analysis Plan

### 4.1 Recruitment Details

Details about patient enrolment, follow-up and inclusion in analysis will be provided using a consort diagram (Figure 2).

Recruitment will be summarised by a breakdown of the reasons for exclusion in tabular form.

### 4.2 Baseline Characteristics

Baseline characteristics, including demographics, medical history, ulcer history, and details of current ulcers will be summarised by treatment group using appropriate descriptive statistics for all randomised participants defined in 2.2 (Table 1, Table 2, Table 3 and Table 4).

### 4.3 Treatment Summary

Type of endovenous treatment received (Endothermal alone, Foam sclerotherapy alone, Mechanochemical alone (MOCA), Endothermal plus Foam, or MOCA plus Foam) will be summarised by treatment group using appropriate descriptive statistics for all randomised participants defined in 2.2 (Table 5).

### 4.4 Primary Endpoints

The primary outcome is time to complete healing and 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 (Table 6). Kaplan-Meier survival curves and the log-ran test will also be presented (Figure 3). As a subsidiary analysis we will investigate the effect of potential confounders listed in section **2.1** (age, ulcer chronicity and ulcer size) on the treatment effect and on time to complete healing using Cox regression, again with centre included in the Cox regression analysis as random effect (Table 6). To assess whether the treatment effect is consistent across all patient sub-groups, the hazard ratios and 95% confidence intervals for treatment from the above Cox regression models (with adjustment for potential confounders and centre as a random effect) will be re-calculated for each of the following subgroups separately; BMI (<23, 23.0-25.0, 25.01-30.0, > 30), Age (≤49, 50-69, 70+), gender (male, female), smoking (Never, previous, current), ulcer size (by quartile), ulcer duration (by quartile), history of deep vein thrombosis (yes, no), history of rheumatoid arthritis (yes, no), taking anti-platelet therapy (yes, no), history of intervention on previous leg ulcer (yes, no intervention, no previous ulcer) and baseline EQ5D (by quartile). The results will be presented using a Forest plot (Figure 4), with the overall result also included at the bottom. We will also use Cox regression to look for differences between the treatment arms by type of endovenous treatment (Endothermal alone, Foam sclerotherapy alone, Mechanochemical alone (MOCA), Endothermal plus Foam, or MOCA plus Foam). Results (hazard ratios and 95% confidence intervals will also be presented graphically in the Forest plot (Figure 5). These subsidiary analyses are intended to provide reassurance that the observed treatment effect is consistent across all patient sub-groups. The study is not powered to detect differences between sub-groups and any observed patterns should be interpreted extremely cautiously, owing to the smaller numbers and increased chance of Type I error. For Cox regression models the proportionality assumption will be assessed graphically (using diagnostic plots) and using Grambsch and Therneau tests and overall fit will be assessed graphically by plotting the Nelson-Aalen cumulative hazard function versus the Cox-Snell residuals and comparing to a 45°reference line.

### 4.5 Ulcer Free Time to 1 year and 24-week Ulcer Healing Rate

Table 7 summarises the ulcer free time to 1 year and 24-week ulcer healing rate between the two arms. In the case that a patient is dead, withdrawn or lost to follow-up before 1 year, ulcer free time will be calculated as the time from randomisation until last follow-up. Multiple linear regression will be used to assess the difference between the treatments arms, with centre as a random effect, before and after adjustment for age, ulcer size and ulcer chronicity (Table 8). Graphical methods will be used to assess whether the assumption of normality is met. If the assumption of normality is not met, and there is no suitable transformation, ulcer free time will be categorized (by quartiles) and the analysis will instead be performed using ordinal regression. Model fit will be assessed using residual plots and/or goodness-of-fit tests, as appropriate. The 24-week healing rate and associated 95% confidence interval will be obtained from the Kaplan-Meier analysis (4.3). The primary analysis will be based on study participants with at least 1 year of follow up only (as explained in 2.2). As a sensitivity analysis we will repeat the above regression model (adjusted for age, ulcer size and ulcer chronicity, and centre) using all the study participants, irrespective of length of follow up.

To assess whether the treatment effect on ulcer free time is the same across all patient sub-groups, the coefficients and 95% confidence intervals for the treatment effect from the above multiple linear (or ordinal) regression model (based on study participants with follow up of at least 1 year) will be re-calculated for each of the following subgroups separately; BMI (<23, 23.0-25.0, 25.01-30.0, > 30), age (≤49, 50-69, 70+), gender (male, female), smoking (Never, previous, current), ulcer size (by quartile), ulcer duration (by quartile), history of deep vein thrombosis (yes, no), history of rheumatoid arthritis (yes, no), taking anti-platelet therapy (yes, no), history of intervention on previous leg ulcer (yes, no intervention, no previous ulcer) and baseline EQ5D (by quartile). The results of this subgroup analysis will be presented in a Forest plot with the overall result also included at the bottom (Figure 6). Differences between the treatment arms by type of endovenous treatment (Endothermal alone, Foam sclerotherapy alone, Mechanochemical alone (MOCA), Endothermal plus Foam, or MOCA plus Foam) will also be investigated and the results (model coefficients and 95% confidence intervals) will be presented graphically in the Forest plot (Figure 7). These subsidiary analyses are intended to provide reassurance that the observed treatment effect is consistent across all patient sub-groups. The study is not powered to detect differences between sub-groups and any observed

patterns will be interpreted extremely cautiously, owing to the smaller numbers and increased chance of Type I error.

### 4.6 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[3]. The SF-36 will be scored using Health Outcome Scoring Software 4.0 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 index-based values ('utilities') will be calculated by the EQ-5D-5L Crosswalk Index Value Calculator downloaded from the EQ-5D official website.

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 (Figures 8-10). Depending on the distribution of the data, the means and 95% CI of means or medians and inter-quartile ranges at baseline, 6-weeks, 6-months and 12-months after randomisation, will be reported (Table 9). Analysis of variance will be used to explore changes in QoL over time and assess the difference between the two intervention groups.

### 4.7 Markers for Clinical Success

Clinical success will be assessed using the Venous Clinical Severity Score (VCSS), which is measured at baseline and 6 weeks post-randomisation. The change in clinical classification in the Clinical, Etiologic, Anatomic, Pathophysiological (CEAP) score at 6 weeks post-randomization from baseline will be reported and the chi-square test will be used to compare between the two arms. Similarly, change in VCSS score will be compared between the two arms using the t-test (assuming change in VCSS is normally distributed) or appropriate non-parametric test (if change in VCSS is not normally distributed).

Table 10 shows the proportions of patients with downgrade of clinical classification from C6 to C5 at 6-weeks post-randomisation and VCSS score. The VCSS scores at 6 weeks post-randomization and baseline will be summarised using boxplot for both arms (Figure 11).

### 4.8 Safety Data

The safety data, including adverse events (AEs) and serious adverse events (SAEs) will be provided in a tabular format for the two arms (Table 11 and Table 12). AEs will be summarised by description and outcome and SAEs will be summarised by SAE reason, frequency, severity, and relationship to treatment, outcome and expectedness.

### 4.9 Derived Variables

1. Deep vein reflux is defined as iliac, femoral, popliteal or crural deep vein reflux detected by Duplex scan.
2. Deep vein obstruction is defined as iliac, femoral, popliteal or crural deep vein outflow obstruction detected by Duplex scan.
3. Time to ulcer healing will be calculated as the difference between the final healing date and date of randomisation. Final healing date is collected in the InForm database and this variable is entered by trial manager after experts agree on the healing date. Patients will be censored at the time of last follow-up if they are dead, withdrawn or lost to follow-up before primary ulcer healing. The follow-up time is one year after randomisation and thus patients with unhealed primary ulcer at one year after randomisation will be also censored.
4. One-year ulcer free time will be calculated as total follow-up time in days (i.e. one year or time to the last follow-up if patients are dead, withdrawn or lost to follow before one year) deducting the total duration of ulcers, including primary ulcer and recurrences.
5. Ulcer chronicity will be calculated as the difference between the date of current ulcer appeared and the date of randomisation.

## 5. Sensitivity analysis

As a sensitivity analysis, we will perform a per-protocol analysis by excluding patients with protocol violations. This sensitivity analysis will cover all primary and secondary outcomes. As the per-protocol analysis leads to the optimal effect of EVRA and could bring attrition bias, we will interpret the results of pre-protocol analysis with extreme caution. The surgeon data is collected separately and not included in the InForm database. If the surgeon data can be merged into the main database and, we will carry out another sensitivity analysis by including surgeon as a random effect in the Cox regression analysis for primary outcome.

**Tables**

Table 1 Baseline characteristics between the EVRA and standard treatment group*

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **Age** | | |
| **Height** | | |
| **Weight** | | |
| **BMI** | | |
| **Gender** | | |
| Male | | |
| Female | | |
| **Smoking** | | |
| Never | | |
| Former | | |
| Current | | |
| **Ethnicity** | | |
| White | | |
| Mixed | | |
| Asian | | |
| Black | | |
| Chinese | | |
| Other | | |
| **EQ-5D** | | |
| Mobility | | |
| Self-care | | |
| Usual activities | | |
| Pain/discomfort | | |
| Anxiety/depression | | |
| Health state score | | |
| **SF-36** | | |
| Physical function | | |
| Role-Physical | | |
| Body pain | | |
| General Health | | |
| Vitality | | |
| Social Functioning | | |
| Role-Emotional | | |
| Mental Health | | |
| **Total AVVQ** | | |

* *Data presented as frequency (percentage) for categorical variables and mean (SD) for continuous variables*

Table 2 Summary of medical history & concurrent medication*

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **Previous pregnancy**† | | |
| Yes | | |
| *History of DVT in pregnancy (yes)* | | |
| No | | |
| **Hormone therapy**† | | |
| None | | |
| Previous HRT | | |
| Current HRT | | |
| Previous OC | | |
| Current OC | | |
| **Previous Rheumatoid disease (yes)** | | |
| **Previous DVT** | | |
| **Current antiplatelet therapy** | | |
| None | | |
| Aspirin | | |
| Clopidogrel | | |
| Other | | |
| **Current anticoagulation therapy** | | |
| None | | |
| Warfarin | | |
| New oral anticoagulants | | |
| Other | | |
| **Current Steroids** | | |
| Yes | | |
| No | | |
| **Current Trental (pentoxifylline)** | | |
| Yes | | |
| No | | |
| **Diabetes** | | |
| Yes | | |
| No | | |

* *Data presented as frequency (percentage) for categorical variables*

† *Female only*

Table 3 Summary of ulcer history*

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **Previous ulcer (yes)** | | |
| **Ulcer dressing** | | |
| NA | | |
| Inadine | | |
| Other | | |
| **Baseline Compression** | | |
| None | | |
| KTwo | | |
| Three-layer bandage | | |
| Four-layer bandage | | |
| European short stretch | | |
| Stocking | | |
| Other | | |
| **Time of wearing** | | |
| Day & night | | |
| Day only | | |

* *Data presented as frequency (percentage) for categorical variables*

Table 4 Characteristics of current ulcer*

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **Time since ulcer diagnosis (months)** | | |
| **Trial ulcer leg** | | |
| Right | | |
| Left | | |
| **Ulcer location** | | |
| Lateral | | |
| Medial | | |
| Circumferential | | |
| **Ulcer size (cm2)** | | |
| **Duplex Scan: Deep Vein** | | |
| Normal | | |
| Abnormal† | | |
| *Reflux* | | |
| *Outflow obstruction* | | |
| **CEAP Score** | | |
| Clinical signs – grade | | |
| $C_5$ | | |
| $C_6$ | | |
| **Clinical signs – presentation** | | |
| Asymptomatic | | |
| Symptomatic | | |
| **Etiologic classification** | | |
| Primary | | |
| Secondary | | |
| Deep | | |
| No venous cause | | |
| **Anatomic distribution** | | |
| Superficial | | |
| Perforator | | |
| Deep | | |
| **Pathophysiologic dysfunction** | | |
| Reflux | | |
| Obstruction | | |
| Both | | |
| No venous cause | | |
| **VCSS Score** | | |
| **Palpable pedal pulses** | | |
| Yes | | |
| No | | |

* *Data presented as frequency (percentage) for categorical variables and median (range) for continuous variables*

[†] *A patient can have both deep vein reflux and obstruction*

Table 5 Treatment summary

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| Endothermal only | | |
| Foam only | | |
| Mechanochemical ablation (MOCA) only | | |
| Endothermal and Foam | | |
| MOCA and Foam | | |

* *Data presented as frequency (percentage)*

Table 6 Time to ulcer healing in patients with chronic venous ulceration (Cox regression model)

| | **Univariate model*** | | **Multivariate model†** | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| **Treatment** | | | | |
| Standard arm | | | | |
| EVRA | | | | |
| **Age (yrs)** | | | | |
| **Ulcer chronicity (mths)** | | | | |
| **Ulcer size** | | | | |
| 1st Quartile | | | | |
| 2nd Quartile | | | | |
| 3rd Quartile | | | | |
| 4th Quartile | | | | |

* *Adjusted by centre (centre included in the model as a random effect)*

† *Adjusted by centre, age, ulcer size and chronicity (centre included in the model as random effect and age, ulcer size and chronicity as fixed effects).*

Table 7 Summary of 12-week and 24-week ulcer healing rate and ulcer free time*

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **12-week ulcer healing rate** | | |
| **24-week ulcer healing rate** | | |
| **No. of patients with recurrent ulcer** | | |
| **Ulcer free time** | | |

* *Data presented as frequency (percentage) for categorical variables and median (range) for continuous variables*

Table 8 Multiple linear regression (ordinal regression) for ulcer free time (days) to 1 year in patients with chronic venous ulceration

| | **Univariate model*** | | **Multivariate model†** | |
|---|---|---|---|---|
| | Coefficient (95% CI) | P value | Coefficient (95% CI) | P value |
| **Treatment** | | | | |
| Standard arm | | | | |
| EVRA | | | | |
| **Age (yrs)** | | | | |
| **Ulcer chronicity (mths)** | | | | |
| **Ulcer size** | | | | |
| 1st Quartile | | | | |
| 2nd Quartile | | | | |
| 3rd Quartile | | | | |
| 4th Quartile | | | | |

* *Adjusted by centre (centre included in the model as a random effect)*

† *Adjusted by centre, age, ulcer size and chronicity (centre included in the model as random effect and age, ulcer size and chronicity as fixed effects).*

Table 9 Summary of quality of life (AVVQ, EQ-5D, SF36) at baseline, 6 weeks, 6 months and 12 months after randomisation

| | | EVRA | Standard |
|---|---|---|---|
| | N | Mean (SD) | Mean (SD) |
| **AVVQ** | | | |
| Baseline | | | |
| 6 weeks | | | |
| 6 months | | | |
| 12 months | | | |
| **EQ-5D health score** | | | |
| Baseline | | | |
| 6 weeks | | | |
| 6 months | | | |
| 12 months | | | |
| **EQ-5D index value** | | | |
| Baseline | | | |
| 6 weeks | | | |
| 6 months | | | |
| 12 months | | | |
| **SF-36 physical health** | | | |
| Baseline | | | |
| 6 weeks | | | |
| 6 months | | | |
| 12 months | | | |
| **SF-36 mental health** | | | |
| Baseline | | | |
| 6 weeks | | | |
| 6 months | | | |
| 12 months | | | |

* *Data presented as mean (SD) or median (IQR), as appropriate*

Table 10 Summary of clinical success at 6 weeks after randomisation

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **VCSS total score** | | |
| Yes | | |
| No | | |

[*] *Data presented as frequency (percentage) for categorical variables*

Table 11 Summary of adverse events

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **No. surgical procedures** | | |
| **Total number of AEs** | | |
| **Description of AE** | | |
| Systemic | | |
| Local | | |
| **Outcome** | | |
| Recovered | | |
| Not yet recovered | | |
| Death | | |
| Unknown | | |
| Missing | | |

[*] *Data presented as frequency (percentage) for categorical variables*

Table 12 Summary of serious adverse events

| | EVRA | Standard |
|---|---|---|
| | N= | N= |
| **No. surgical procedures** | | |
| **Total number of SAEs** | | |
| **Serious reason** | | |
| Death | | |
| Life threatening | | |
| Persistently disabling | | |
| Hospitalisation required | | |
| Congenital abnormality | | |
| Other | | |
| **Frequency** | | |
| Single Episode | | |
| Intermittent | | |
| Frequent | | |
| Continuous | | |
| Unknown | | |
| **Severity** | | |
| Mild | | |
| Moderate | | |
| Severe | | |
| Life threatening or disabling | | |
| **Relation to procedure** | | |
| Not related | | |
| Unlikely | | |
| Possible | | |
| Probable | | |
| Definite | | |
| **Outcome** | | |
| Recovered | | |
| Not yet recovered | | |
| Death | | |
| Unknown | | |
| **Expectedness** | | |
| Expected | | |
| Unexpected | | |

[*] *Data presented as frequency (percentage) for categorical variables*

**Figures**

**Reference**

1. Kulkarni SR, Slim FJ, Emerson LG, Davies C, Bulbulia RA, Whyman MR, et al. Effect of foam sclerotherapy on healing and long-term recurrence in chronic venous leg ulcers. Phlebology 2012.

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3. Ward A, Abisi S, Braithwaite BD. An online patient completed Aberdeen Varicose Vein Questionnaire can help to guide primary care referrals. Eur J Vasc Endovasc Surg 2013;45(2):178-82.