A randomized trial of early Endovenous Ablation in Venous Ulceration

EVRA Trial Investigators

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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Gohel MS, Heatley F, Liu X, et al. A randomized trial of early endovenous ablation in venous ulceration. N Engl J Med. DOI: 10.1056/NEJMoa1801214

This supplement contains the following items:

1. Original protocol (V1.0), final protocol (V5.0), summary of changes.
2. Original statistical analysis plan (V2.0), final statistical analysis plan (V4.0), summary of changes

Supplement table of contents

EVRA (Early Venous Reflux Ablation) ulcer trial

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

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	Date	**Signature**
Protocol authorised by: Name: Professor Alun H Davies	**27th June 2013**	

Study Management Group

Chief Investigator: Professor Alun H Davies

Co-investigators: Mr Manjit S Gohel, Mr Richard Bulbulia, Mr Keith R Poskitt, Professor Andrew Bradbury, Professor Nicky Cullum, Miss Sophie R Renton, Mr I Nyamekye

Statistician: Dr Jane Warwick

Health economist: Dr David Epstein

Study Management: Miss Francine M Heatley

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Miss Francine M Heatley

Address: Vascular Surgery Research Group , Room 4N12, 4th Floor North Wing

Charing Cross Hospital, Fulham Palace Road, London W6 8RF

Tel: 020 3311 7371

E-mail: f.heatley@imperial.ac.uk

Fax: 0203 3117362

Web address: www.evrastudy.org

Clinical Queries

Clinical queries should be directed to either the Local PI or the Study Coordinator who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office

Imperial College London and Imperial College Healthcare NHS Trust

Room 5L10C, 5th Floor Lab Block

Charing Cross Hospital

Fulham Palace Road

London, W6 8RF

Tel: 0203 311 0204

Fax: 020 311 0203

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This protocol describes the EVRA study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, UK Clinical Trials Regulations, the Data Protection Act and other regulatory requirements as appropriate.

1. INTRODUCTION

1.1 BACKGROUND

Chronic leg ulcers are open "sores" on the lower limbs situated between the ankles and knees, which fail to heal within 6 weeks. These ulcers represent a source of great discomfort and social isolation to patients who often complain of associated pain, odour and wound discharge. The time taken for the ulcers to heal means that the condition is also particularly frustrating to health carers involved in their management in hospital and community settings. 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[1]. 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[2 3]. 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[4]. It should also be noted that with an aging and increasingly obese population[5], the incidence and prevalence of venous ulceration are both likely to increase. Treatment of the condition in the UK produces a substantial cost burden estimated at £400-600 million per annum[6].

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%[7 8], and the true population healing rates are likely to be significantly lower. Some patients may never heal and those that do heal are at high risk of recurrent ulceration. These poor outcomes are likely to be a reflection of the severe underlying venous dysfunction in this patient group, although inadequate assessment and suboptimal treatment are also likely to be important contributing factors.

1.1.1 Pathophysiology of venous ulceration

The venous circulation of the lower limb has two components, the deep and superficial systems. Blood normally flows from the superficial to the deep veins and is prevented from flowing back down the leg under the influence of gravity by 'one-way' valves along the veins. When these valves become incompetent (leaky), the superficial veins usually become dilated and tortuous (varicose) and the resulting sustained high venous and capillary pressures lead to skin inflammation and ulceration (breakdown of skin). The deep veins also have valves, which may also become incompetent, but are not visible on the skin. Duplex ultrasound studies[9 10 11] on patients in leg ulcer clinics suggest that:

- Around 50% of patients with venous leg ulcers have diseased superficial veins alone, with a further 30-40% having a mixture of superficial and deep venous disease. Both of these groups of patients benefit from correction of their

superficial venous reflux, which has been shown to reduce the risk of ulcer recurrence[12].

- A minority (5-10%) of patients with venous ulcers have diseased deep venous systems only, and are not amenable to surgical correction. These patients are usually treated with compression bandaging alone

Ulcer healing strategies are based on efforts to reduce this leakage (reflux) of blood back down the leg and into the skin, as this is considered the most significant cause of high venous pressure in most patients. Longstanding venous hypertension has been shown to cause a number of changes to the microcirculation in the lower leg, which can contribute to the chronic skin changes or eventual ulceration associated with chronic venous disease[13]. Compression bandaging to the leg (which may need to be re-applied 1-4 times per week) counteracts the gravitational force on the blood, in effect temporarily replacing the incompetent valves[14]. Diseased superficial veins can be surgically removed (open varicose vein surgery) or ablated using endovenous interventions (see below) without harming the overall venous function of the leg, theoretically removing a causative factor for recurrence of the ulcer after the compression bandaging has ceased. The deep vein defects are not generally amenable to surgery.

1.1.2 Treatment options for superficial venous reflux

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[15]. 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. Long-term studies have also identified significant complications of open surgery including nerve damage and recurrence of varicose veins, seen in over 60% of patients at 11 years in one randomized study[16].

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. Interventions such as ultrasound guided foam sclerotherapy (UGFS)[17], endovenous laser (EVLA)[18] or radiofrequency ablation (RFA)[19] can be performed using local anaesthesia in an outpatient setting. These treatments involve cannulation of the vein to be treated (usually under ultrasound guidance) and obliteration of the venous channel by either chemical ablation (using foam sclerosant), or thermal ablation (using a laser or radiofrequency fibre). Numerous randomized studies have demonstrated that endovenous modalities are, at worst, comparable to open surgery in terms of recurrence (and likely to be better), but clearly superior in terms of pain, bruising and other early complications[20-22]. Each of the different endovenous modalities has advantages and potential disadvantages, although all are less invasive than traditional open surgery. This is of particular relevance to patients with

chronic venous ulceration, who are often elderly, have extensive co-morbidities and may be reluctant to undergo surgical procedures involving general anaesthesia. Endovenous techniques can also be performed without discontinuing anti-coagulation therapy, which is increasingly prescribed in this patient population.

1.1.3 Summary of current research

The most significant study of superficial venous intervention in patients with venous ulceration is the ESCHAR study (Barwell, Poskitt; Lancet 2004 & Gohel, Poskitt; BMJ 2007)[7 12]. The study aimed to evaluate the role of traditional superficial venous surgery in reducing ulcer recurrence in patients with open or recently healed venous ulcers. Following prospective observational studies to inform power calculations, a total of 500 patients were randomized to compression therapy alone or compression with open surgery for superficial venous reflux. The group randomized to surgical treatment had significantly lower venous ulcer recurrence rates at 4 years (Figure 1).

Analysis stratified by pattern of venous reflux demonstrated that this clinical benefit was present for patients with isolated superficial venous reflux and patients with superficial and segmental deep reflux. This clearly indicated that the majority of patients with chronic venous ulceration could benefit from superficial venous intervention. As a result, the current optimal management of patients with venous ulceration includes the treatment of refluxing superficial veins to reduce the risk of ulcer recurrence[23].

Analysis of ulcer healing within the ESCHAR trial demonstrated that there was no significant improvement in ulcer healing rates for the group randomized to compression plus surgery (Figure 2). This finding has led many to conclude that treatment of venous reflux does not have a role in patients with open ulcers.

Figure 1. ESCHAR trial – ulcer recurrence

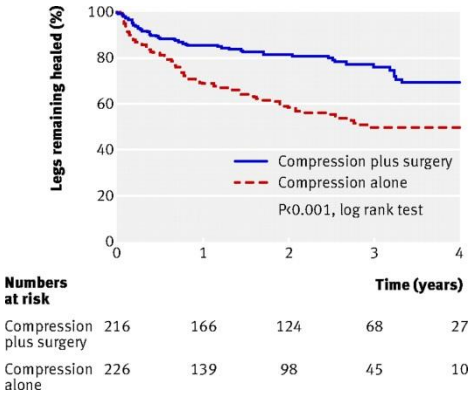
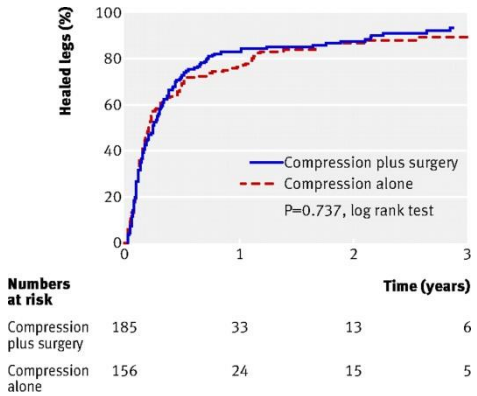


Figure 2. ESCHAR trial – ulcer healing



However, the ESCHAR study was designed and powered to assess ulcer recurrence rather than healing, and the statistical power of this trial was further weakened by a high cross-over rate, as around a quarter of patients randomized to surgery subsequently refused to have an operation. This highlights the need for a minimally invasive superficial venous treatment modality in this patient group. In addition, the

median time to treatment within the study was around 2 months, by which time smaller ulcers may have already healed with compression bandaging, and, in many cases, the surgical procedures used were suboptimal when judged by current standards. Consequently, it is plausible that the benefits of treating superficial venous reflux were underestimated in this study, particularly for the assessment of ulcer healing.

In a smaller Dutch randomized trial, 170 patients (200 legs) were randomized to compression alone or compression with surgical treatment of superficial reflux (including subfascial endoscopic perforator surgery – SEPS)[8]. Although results did not reach statistical significance, there was a clear trend towards improved ulcer healing rates and greater ulcer free time in the group randomized to surgery.

Despite the widespread acceptance of endovenous modalities, few prospective studies have been published reporting outcomes after endovenous treatment in patients with leg ulcers. In a prospective study of 186 patients with leg ulceration treated with UGFS, the ulcer healing rate was over 70% and the patient acceptability of treatment was excellent (Poskitt et al)[24]. In a further study of foam sclerotherapy in 130 patients, a healing rate of 82% was achieved (Bradbury et al)[25]. Whilst these small non-randomized studies lend support to our hypothesis that early intervention to correct superficial venous reflux will promote ulcer healing, a large randomized trial is required to provide reliable evidence and thus change practice.

1.2 RATIONALE FOR CURRENT STUDY

Whilst the management of patients with venous ulcers has evolved in recent years and ulcer healing and recurrence rates have shown some improvement, we believe that there is a strong argument in favour of this study at this time for the following reasons:

- The prevalence of venous ulceration is likely to increase, particularly with an aging and increasingly obese population. In view of the significant financial and psychosocial costs of venous ulceration, it is imperative that the optimal treatment strategies are identified.
- Despite numerous studies of topical ulcer treatments, the only treatment shown to improve venous ulcer healing is compression bandaging. Compression supports the venous circulation, but is poorly tolerated by some patients and does not address the underlying problem of venous reflux. The intervention in this proposal involves treating the underlying anatomical venous disorder using effective, minimally invasive endovenous interventions and offers a logical, deliverable and long-term approach to reducing venous hypertension.
- The treatment of superficial venous reflux has been transformed in recent years through the widespread use of minimally invasive, endovenous interventions, which patients find more acceptable than traditional open surgery.

- Ablation of superficial reflux should be considered in all patients with leg ulcers and superficial venous reflux, but if early intervention is associated with moderate improvements in ulcer healing compared to deferred intervention (i.e. post-healing), significant cost savings could be realised.
- Patients find venous leg ulcers painful, distressing and a significant inhibition to normal, independent life. Interventions to reduce the time to healing could reduce patient distress and significantly improve quality of life.

Therefore, we believe that there is a cogent argument for conducting this trial at this time. 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. The research team has a strong track record in relevant research areas and includes clinicians and researchers who successfully completed the landmark clinical trial on which this proposal is based (ESCHAR trial), and numerous other high impact clinical trials evaluating treatments in venous ulceration.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

What is 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?

2.2 SECONDARY OBJECTIVES

To investigate:

- The ulcer free time to 1 year
- The technical success of endovenous interventions

3. PARTICIPANT ENTRY

3.1 PRE-REGISTRATION EVALUATIONS

Prior to commencing, information will be disseminated to GP practices in each recruiting region and meetings will be arranged with key community nursing staff and at leg ulcer clinics to promote the trial. Patients would be referred to secondary care as part of the standard care pathway.

At the referral visit patients will be given an appropriate time period to consider participation (at least 24 hours). Written consent will be obtained from those patients who agree to participate and randomization will be performed using the online service. For patients randomized to endovenous ablation of superficial venous reflux, a date for intervention will be booked as soon as possible (i.e. within 2 weeks). At each recruiting centre, an online log of all screened patients will be kept using the InForm system. Basic demographic data and reasons for non-eligibility will be recorded. Whilst participant baseline characteristics may vary slightly across recruiting sites, randomized treatment allocation will allow reliable assessment of the effects of early versus delayed endovenous ablation in ulcer healing.

3.2 INCLUSION CRITERIA

- Current leg ulceration of greater than 6 weeks, but less than 6 months duration
- Able to give informed consent to participate in the study after reading the patient information documentation
- Patient age > 18 years
- Ankle Brachial Pressure Index (ABPI) $\geq$ 0.8
- Superficial venous disease on colour duplex assessment deemed to be significant enough to warrant ablation by the treating clinician (either primary or recurrent venous reflux)

Patients who cannot speak / understand English will be eligible for inclusion and informed consent will be obtained with assistance from translation services as per standard clinical practice. In view of the lack of cross-cultural validation for quality of life tools, only healing outcome data will be collected.

3.3 EXCLUSION CRITERIA

- Presence of deep venous occlusive disease or other conditions precluding superficial venous intervention (at the discretion of local research team)
- Patients who are unable to tolerate any multilayer compression bandaging will be excluded. However, concordance with compression therapy can be variable for patients at different times. Patients who are generally compliant with compression, but unable to tolerate the bandages for short periods will still be eligible to inclusion. A period of non-compliance with compression bandages will not be considered a protocol violation, but a normal variation within the spectrum of ‘standard therapy’.

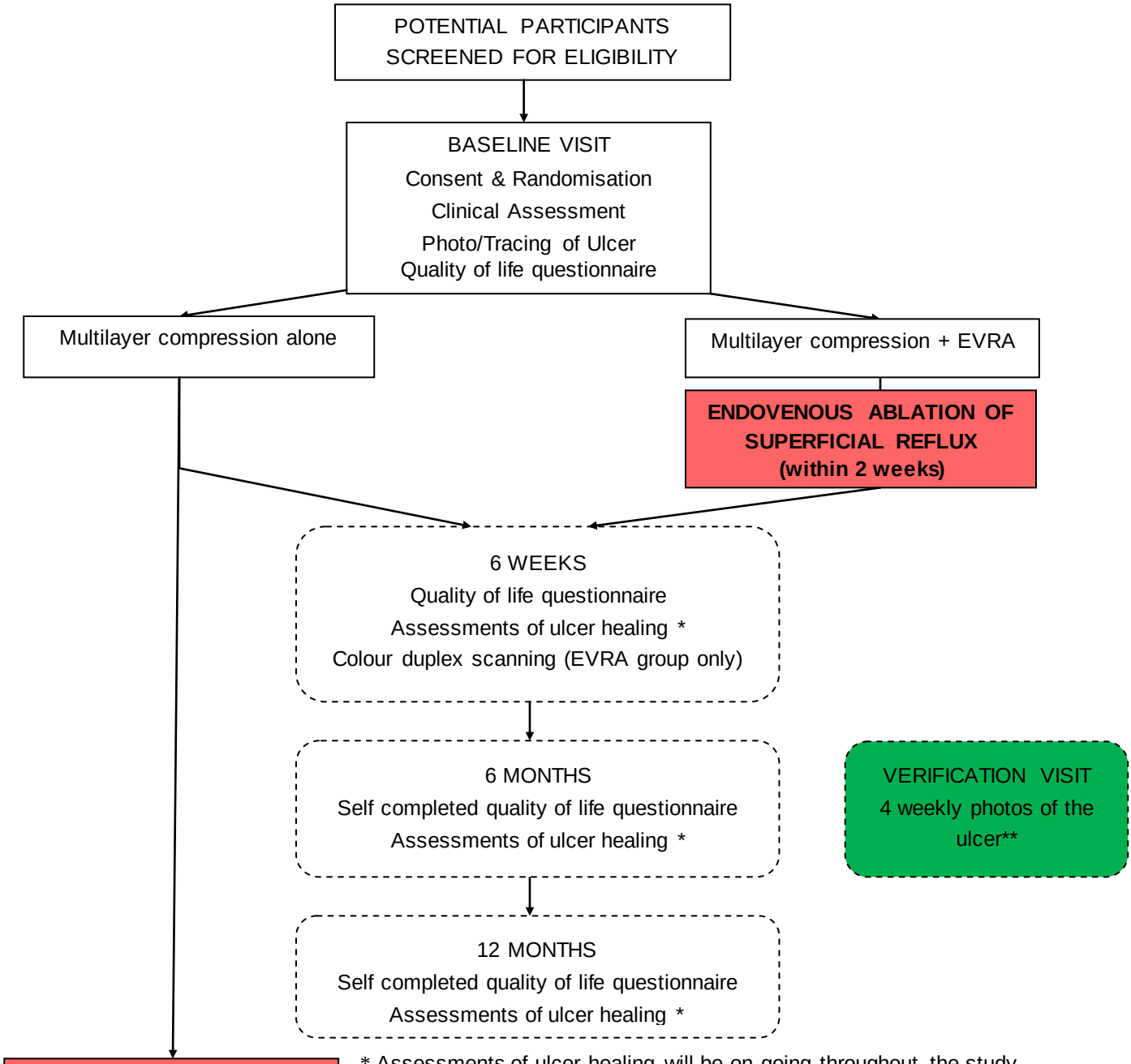
- Inability of the patient to receive prompt endovenous intervention by recruiting centre
- Pregnancy (female participants of reproductive age will be eligible for inclusion in the study, subject to a negative pregnancy test prior to randomisation)
- Leg ulcer of non-venous aetiology (as assessed by responsible clinician)
- If patient is deemed to require skin grafting they cannot be included

4. STUDY DESIGN

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

1. 'Standard' therapy consisting of multilayer elastic compression bandaging with deferred treatment of superficial reflux (usually once the ulcer has healed)
2. Early endovenous treatment of superficial venous reflux (within 2 weeks) in addition to standard therapy

The study design is summarised in Figure 3 below.



* Assessments of ulcer healing will be on going throughout the study follow-up period and will be performed by community nursing teams and research staff (at least every month)

**Once the research team has been informed by the patient that the ulcer has healed. Can occur any time during the 12 months.

4.1 PATIENT RANDOMIZATION

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 – see 4.3.1). 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.

4.2 STUDY SETTING

Eligible patients with chronic venous ulcers will be recruited from the following centres:

1. Imperial College Healthcare NHS Trust (PI: Professor AH Davies)
2. Cambridge University Hospitals NHS Foundation Trust (PI: Mr MS Gohel)
3. Gloucestershire Hospitals NHS Foundation Trust (PI: Mr KR Poskitt)
4. West Midlands Vascular Research Collaborative (Heart of England NHS Trust; University Hospital Birmingham NHS Trust; City and Sandwell NHS Trust; Russell's Hall Hospital NHS Trust, Dudley; and New Cross Hospital NHS Trust, Wolverhampton) (PI: Professor A Bradbury)
5. North West London Hospitals NHS Trust (PI: Miss SR Renton)
6. Worcestershire Acute Hospitals NHS Trust (PI: Mr I Nyamekye)

4.3 STUDY OUTCOME MEASURES

4.3.1 Primary outcome measure

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 randomized leg. Community or hospital healthcare staff, depending on the local model of care, will perform assessment of ulcer healing.

Data on the status of the reference leg will be collected throughout the study by research staff scrutinising community medical / nursing records and contacting the patient / community nursing teams by telephone (on a monthly basis at least).

If either the community nursing / medical staff or the patient believe that ulcer healing (defined as complete re-epithelialisation of the ulcerated leg) has been achieved, they will be asked to contact the local research centre immediately. This notification of possible ulcer healing will constitute a 'trigger' for the research staff at the recruiting centre to arrange an urgent verification assessment by a member of the healthcare team (within 1 week).

Verification will be by clinical assessment and digital photography, to be repeated weekly for 4 weeks. The digital images will be evaluated by two blinded expert assessors in order to ascertain the date of healing, which will be considered the primary healing end-point. Disagreements will be resolved through discussion with involvement of a third blinded expert reviewer if necessary. This approach will be applied to patients in both treatment arms and is consistent with the methods utilized in other large HTA funded leg ulcer trials (e.g. VenUS IV). Legs deemed to have an open ulcer on clinical assessment would continue within the study. If healing is confirmed by clinical and blinded photograph assessments at the first verification visit, the date of healing notification (by patient or community nurse) will be taken as the date of ulcer healing.

4.3.2 Secondary outcome measures

A number of secondary outcome measures will be evaluated in the EVRA study:

1. Ulcer Healing Rate: Healing rate will be evaluated in addition to time to ulcer healing to allow comparison with other published studies.
2. Ulcer Free Time: Will be calculated up to 1 year for each study arm. This will allow a very practical and easily understood assessment of the clinical difference between the 2 arms of the study. This will also allow comparison with other studies that have reported this outcome. In order to facilitate accurate calculation of ulcer free time, clinical follow up will be continued after ulcer healing up to 1 year after randomisation.
3. 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. The 6-week questionnaire will be given to the patient at the follow-up appointment, whereas other QoL questionnaires will be sent to the patient. AVVQ is the most widely utilised disease specific QoL tool in venous disease and has been extensively validated. A score out of 100 points is calculated, with a higher score indicating more severe QoL impairment. Changes in QoL scores will offer a comparison with other studies and, in the standard treatment arm, will allow an assessment of the natural history of venous ulceration treated with compression.
4. Health Economic Assessment: Cost items in hospital and community care will be recorded for each patient. Standard HRG published tariffs will be used to calculate overall costs. A standard tariff will be applied for each bandage change, although additional treatments administered for the treatment of symptoms or

complications directly related to venous ulceration will be included. Utilities (QALYs) will be calculated from generic QoL questionnaire and cost-effectiveness will be analysed.

5. Other Markers Of Clinical Success: The Venous Clinical Severity Score (VCSS) 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.

4.4 DURATION OF FOLLOW-UP

In the present study, participants will be followed-up until either:

1. 1 year post-randomization
2. Patient choice to withdraw from the study. Patients who no longer wish to complete quality of life questionnaires will be asked if they would object to the use of healing status data (to contribute to the primary outcome)
3. Death

In order to allow assessment of ulcer free time to 1 year, patients with healed ulcers will be evaluated using telephone follow-up (performed by staff at the recruiting centre) on a monthly basis until 1 year. The aim of the telephone follow-up will be to confirm that the ulcer remains healed, or in cases of ulcer recurrence, to ascertain the date of recurrence and of subsequent healing. More prolonged post-intervention follow-up for several years is required to obtain reliable long-term recurrence rates in both treatment groups. Accordingly, participants will be asked to consent to long-term follow-up at the outset, and funding for an extension to EVRA will be sought in due course.

4.5 STUDY DURATION

The EVRA study will take four years to complete. The overall study timetable is summarised in Figure 4.

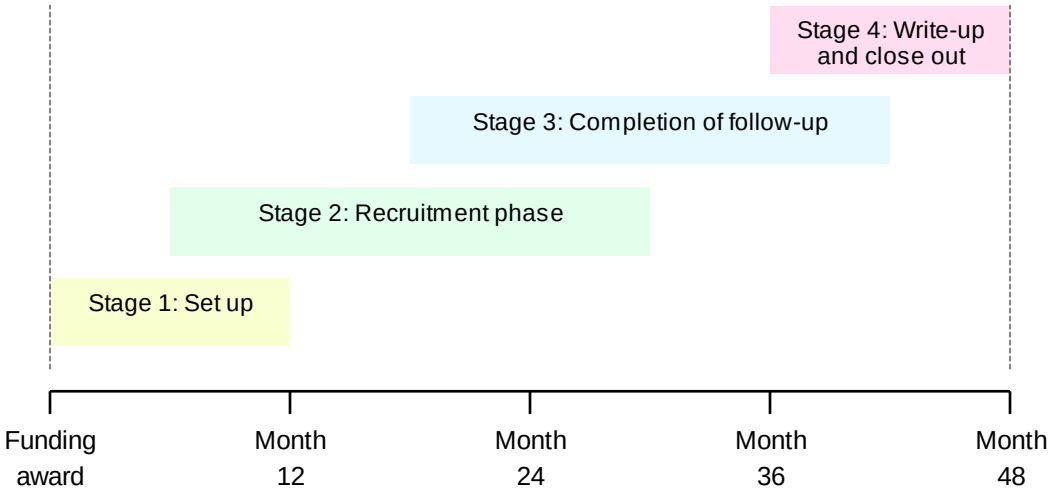


Figure 4. EVRA study Gantt chart

5. DETAILS OF INTERVENTIONS

5.1 VARIATIONS IN ENDOVENOUS INTERVENTIONS

A wide range of endovenous treatment modalities are now available and in widespread use for the ablation of superficial venous reflux. These include:

- Endovenous thermal ablation using laser or radiofrequency
- Ultrasound guided foam sclerotherapy (UGFS)
- Other endovenous interventions such as mechanochemical ablation, steam ablation and glue
- Any combination of the above treatments

In addition to the different modalities in use, the treatment strategy may also vary between institutions and between individual clinicians within the same department. Variations may occur in:

- Site of vein cannulation (and therefore the length of vein ablated)
- Location of treatment ('office' or clinic based versus operating theatre)
- Treatment strategy for sub-ulcer venous plexus (to ablate or not)
- The treatment of visible varicose veins (no treatment, UGFS or surgical avulsion) and the timing of any intervention

5.2 STANDARDISATION OF INTERVENTIONS IN EVRA STUDY

With the lack of consensus on a single, optimal endovenous treatment strategy for superficial reflux in patients with leg ulceration, perfect standardisation of interventions will be impossible. All endovenous interventions should be performed as deemed to be 'optimal' by the treating clinician for each individual patient, with the following stipulations:

1. The endovenous strategy must include ablation of the main truncal venous reflux
2. Truncal venous reflux should be treated to the lowest point of incompetence, where possible
3. Significant (as deemed by the treating clinician) residual / recurrent superficial reflux on the 6 week duplex scan, should be ablated
4. Patients should continue with multilayer compression immediately after treatment

5.3 STANDARDISATION OF COMPRESSION

Patients will receive the standard compression used in the individual centres prior to ulcer healing following randomisation (this will include four layer bandaging, three layer bandaging, European short stretch, stockings). Post healing the patients will be given compression hosiery in line with local policy.

5.4 FURTHER TREATMENT FOR COMPRESSION ALONE ARM

Patients randomised to multilayer compression alone can be offered endovenous treatment of superficial reflux once healing has been confirmed (see 4.3.1). Endovenous ablation should be performed as per standard practice in the treating centre and details of this will be recorded. Endovenous intervention may also be offered if there is clinical deterioration in the active leg ulcer and it is clinically felt that the patient may benefit from early intervention. This will be recorded on the electronic case report form.

6. ASSESSMENT AND FOLLOW-UP

6.1 PATIENT IDENTIFICATION

Patients will be referred to secondary care for evaluation of the management of their leg ulcer as part of the standard pathway of care.

6.2 REFERRAL VISIT

At the initial visit the patient will be evaluated by clinical assessment and colour duplex examination, which is part of the normal investigation of a patient with leg ulceration. Dependant on the results of these tests, the patient will be asked if they would consider taking part in the trial and approached for consent. The patient will be given a minimum of 24 hours to consider the trial and if willing to participate will return to the leg ulcer clinic to give consent and undergo a baseline visit.

6.3 BASELINE VISIT

Patients will undergo detailed clinical assessment by the research nurse as part of the baseline evaluation (see *Appendix 1*). Recorded assessments will include:

- Demographic details (age, sex, ethnicity)
- Pregnancy test for woman of child bearing potential
- General clinical details (body mass index, ankle brachial pressure index – performed within previous 4 weeks, comorbidities, medication history)
- Ulcer details (duration, progression, previous ulcer history, size of current ulcer – using photography and planimetry)
- Assessment of range of ankle movement
- Details of venous disease (previous deep vein thrombosis, previous venous interventions, pattern of venous reflux on duplex)

Additional assessments will include:

- Assessment of Clinical, Etiologic, Anatomic, Pathophysiological (CEAP) score
- Assessment of venous clinical severity score (VCSS)
- Disease specific (Aberdeen varicose vein questionnaire – AVVQ) and generic (EuroQuol 5D – EQ5D & short form (SF) 36) quality of life assessments

At this visit, eligible and consenting patients will be randomised into the trial.

6.4 FOLLOW-UP ASSESSMENTS

Randomized patients will undergo routine leg ulcer care in community or hospital (or both) settings, in accordance with the local standard. This will equate to wound reviews and dressing changes ranging between once and 4 times per week (depending on the ulcer). The exact nature of dressings and date of dressing change will be documented by community or hospital healthcare professionals. This will

allow an accurate record of the dressing types used and will be collected and verified by the research nurse.

In addition, the following assessments will be conducted:

6.4.1 6-week clinic visit

- Clinical assessment
- In the compression plus early venous reflux ablation group, venous duplex scanning will be performed at 6 weeks post-randomization to verify anatomical treatment success. Depending on the results of the scan, the decision to perform further superficial venous interventions will be left to the discretion of the responsible clinical staff. Irrespective of the number and timing of venous interventions, all analyses will be performed on intention to treat.
- Wound tracing and photo
- Assessments of disease specific and generic quality of life (AVVQ, EQ5D & SF36) by means of self completed questionnaire

6.4.2 Further follow-up

- Assessments of disease specific and generic quality of life (AVVQ, EQ5D & SF36) by means of self completed questionnaire at 6 months and 12 months post-randomization (sent to the patient).
- The research team will perform monthly telephone evaluation of the patient and access the community notes or telephone the community nurses in order to collect and verify the data collected.
- Once the research team has been informed that the ulcer has healed the patient will undergo an urgent verification visit

6.5 URGENT VERIFICATION VISIT

- A member of the local research team will perform the four verification visits to confirm healing. Photographs will be taken and send to the Trials Unit for independent verification.

7. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

7.1 SAMPLE SIZE CALCULATION

The sample size calculation for this study was based on the primary outcome of ulcer healing. The ESCHAR trial was a similar randomized study, which published the final results in 2007 (see 1.1.3). A total of 500 patients with open or recently healed venous ulcers were randomized to standard therapy alone or standard therapy plus open surgery for superficial venous reflux. The study was powered and designed to evaluate differences in ulcer recurrence (rather than healing). Consequently, the median time from randomization to treatment delivery was over 7 weeks. Nevertheless, the 24-week healing rate in patients randomized to standard treatment (compression alone) was approximately 60%. Two recent prospective studies evaluating the early treatment of superficial venous reflux suggested that the 24-week healing rate may be as high as 82%[24 25].

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 with 90% power will therefore require 208 subjects (68 healed leg ulcers) per group (log-rank test). With 10% dropout the study will therefore require 462 subjects (231 in each arm). To incorporate further allowances for protocol violations and unexpected dropouts, the target sample size will be 500 patients.

7.2 PLANNED ANALYSES

Basic descriptive methods will be used to present the data on study participants, trial conduct, clinical outcomes and safety (in total and for each study group separately). The primary outcome will be 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 log-rank test (two-tailed, 5% significance level). Kaplan-Meier survival curves will also be presented and as a subsidiary analysis we will investigate the effect of study centre, participant age, ulcer size and chronicity on time to complete healing using Cox regression. To adjust for potential surgeon and centre effects, surgeon and centre will be included in the Cox regression analysis as random effects. All analyses will be on an intention-to-treat basis. Non-compliance with allocated interventions and other protocol violations will be kept to a minimum. Accordingly, per-protocol analyses are not envisaged, and the chief emphasis will be on the overall result on time to ulcer healing.

7.3 HEALTH ECONOMIC ANALYSIS

The economic evaluation will be based on both a modelling exercise and a patient level in-trial analysis. The analysis will be performed from the perspective of the NHS and society. The economic model will be developed from the model used for another HTA funded project (REACTIV trial)[26]. The model will assess the relative cost-effectiveness (assessed in terms of incremental cost per QALY), of the treatment strategies. The trial data will inform the model and further data (including that for other relevant comparators) will come from the literature and other data sources. Use of secondary and primary care patient resource use and EQ-5D responses will come from the trial. They will be collected by case note review and questionnaires completed at baseline, 6 and 12 months. Unit costs will be based on nationally available data and study-specific estimates. QALYs will be estimated using responses to the EQ-5D. The results of the economic model will be supplemented by an in-trial analysis. The trial analysis will use the estimates of costs and QALYs estimated for each trial participant to calculate the incremental cost-effectiveness ratios for the 12-month follow-up. The results of the analyses will be presented as estimates of mean incremental costs, effects, and, incremental cost per QALY. Sensitivity analysis will be conducted for both model and trial based evaluations. The results of the base case and sensitivity analyses will be presented as mean estimates and as cost-effectiveness acceptability curves (CEACs).

7.4 INTERIM ANALYSES: ROLE OF THE DATA MONITORING COMMITTEE

During the study, interim analyses of all related SAEs and other study outcomes will be supplied in strict confidence to the independent Data Monitoring Committee (DMC). The DMC will request such analyses at a frequency relevant to the stage of the study (typically at 12 monthly intervals with a Chairman's review every 6 months) or in response to emerging data from other trials. 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 interim results until the end of the study.

In the light of these interim analyses and any other information considered relevant, the DMC will advise the Steering Committee if, in their view, the randomized comparisons in the study have provided both (i) "proof beyond reasonable doubt" * that early correction of superficial venous reflux improves ulcer healing; and (ii) evidence that might reasonably be expected to influence materially patient management.

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis for healing may be needed before stopping the trial prematurely. Furthermore, this criterion has the practical advantage that the exact number of interim analysis would be of little importance, so no fixed schedule is proposed.

The DMC would also be expected to advise the Steering Committee if clear evidence emerged of an adverse effect on intervention-related SAEs, and if this hazard seemed likely to outweigh any potential benefit.

7.5 LOSSES TO FOLLOW-UP AND PROTOCOL VIOLATIONS

The primary assessment involves intention-to-treat analysis. Therefore, strenuous efforts will be made to ensure that only patients willing to undergo either immediate or delayed superficial venous ablation and compression bandaging are randomized. Monthly reports of protocol violations will be provided by local sites to the trial coordinators, who reserve the right to suspend or exclude sites in the event of wilful protocol violations. Similarly, efforts will be made to obtain complete follow-up for all randomized participants (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.

We appreciate that a high rate of protocol violations was seen in previous trials of venous ulceration (including the ESCHAR trial). This is likely to reflect the reluctance and apprehension of elderly patients to undergo surgical interventions involving general anaesthesia. The modern management 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 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.

8. ADVERSE EVENTS

8.1 REPORTING PROCEDURES

All serious adverse events and all intervention-related adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

8.2 RELATED ADVERSE EVENTS

Patients randomised to early venous intervention have the potential risks of treatment. Competent, experienced medical staff will perform all procedures and every effort will be made to prevent adverse effects.

Radiofrequency or laser ablation may cause:

- some short-term side effects such as numbness or pins and needles (paraesthesia).
- some tightness in your legs and the affected areas may be bruised and painful.
- nerve injury is also possible, but usually only temporary.

Sclerotherapy can have side effects, including:

- blood clots in other leg veins (DVT)
- headaches
- changes to skin colour, such as, brown patches over the treated veins
- fainting
- temporary vision problems

After any of these procedures, it is possible the patient may develop a painful lump over the varicose veins, known as phlebitis, which may require treatment with antibiotics and/or drainage.

8.3 NON SERIOUS ADVERSE EVENTS

All such events, which are judged by the local PI to be related to the interventions, whether expected or not, should be recorded.

8.4 SERIOUS ADVERSE EVENTS

In addition to clinical assessments, patients will be contacted on a monthly basis by telephone for the duration of the study to identify any additional treatments, admissions or other complications related to their leg ulceration. Unrelated serious adverse events will also be recorded and reported in accordance with the Good Clinical Practice guidance. Serious adverse events (SAE) are defined as those adverse events that: result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; are

cancer; or are other important medical events in the opinion of the responsible investigator (i.e. not life threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or more of the outcomes described previously).

All SAEs reported by participants at (or between) each follow-up visit will be recorded by local researchers in the clinical research form. Any SAE that is considered, with a reasonable probability, to be due to study intervention (i.e. superficial venous ablation) should be reported to the local PI (or their designated deputy) and to the trial coordinator. Such intervention-related SAEs will be reported by the trial coordinators to the Sponsor, Chair of the Data Monitoring Committee and to the relevant Ethics Committee.

Contact details for reporting Intervention-related SAEs

Fax: 0203 311 7362, attention Francine Heatley

Please send SAE forms to: Francine Heatley

Tel: 0203 311 7371 (Mon to Fri 09.00 – 17.00)

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

After approval from the Research Ethics Committee, the study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this study.

9.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.6 FUNDING

The study is funded by the NIHR as part of the HTA programme.

9.7 QUALITY ASSURANCE AND CONTROL

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition). Quality Control will be performed according to the requirements of the Risk Assessment performed by ICTU. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

10. STUDY MANAGEMENT

The study will be coordinated by a trial manager based at ICTU reporting to the Clinical Coordinators (MG and RB) and the Chief Investigator (AD). The Clinical Coordinators will liaise with local principal investigators (L-PI) to ensure that the trial is conducted locally according to protocol and in an expeditious manner. The organisational structure and responsibilities are outlines below.

10.1 PRINCIPAL INVESTIGATORS

The chief investigator and clinical coordinators have overall responsibility for:

- Design and conduct of the study
- Preparation of the Protocol and subsequent revisions
- Managing the Trial Coordinating Centre
- Development of SOPs

10.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established in line with HTA guidance, consisting of the chief investigator, clinical coordinators, trial manager, trial statistician, patient representative, an independent chair and at least 1 other independent member will be formed and will meet on a 6-monthly basis to discuss trial progress. The TSC is responsible for:

- Agreement of the final Protocol
- Agreeing the Data Analysis Plan
- Reviewing progress of the study and, if necessary, agreeing changes to the Protocol
- Reviewing new studies that may be of relevance
- Review and approval of study reports

10.3 DATA MONITORING COMMITTEE

The independent Data Monitoring Committee (DMC) will be established in line with HTA guidance will focus on the rights, safety and well being of study participants. DMC responsibilities are:

- Reviewing unblinded interim data according to the schedule outlined in the Protocol
- Advising the Steering Committee if, in their view, the randomized data provide evidence that may warrant early termination for either safety or efficacy.

10.4 TRIAL COORDINATING CENTRE

The Trial Coordinating Centre (TCC) is responsible for the overall coordination of the Study, including:

- Study planning and organisation of Steering Committee meetings
- Agreement of each local recruitment plan
- Contractual issues with local study sites
- Ethics Committee applications
- Design, implementation and maintenance of IT systems for the study
- Auditing and monitoring of overall progress of the study
- Clinical safety monitoring (including the reporting of all “related” SAEs to the Chair of the DMC and Ethics Committee)
- Liaison with the Data Monitoring Committee and (where appropriate) with regulatory authorities and other outside agencies
- Responding to technical and administrative queries from local study sites

10.5 LOCAL STUDY SITES

The local principal investigators (L-PI) and clinical staff at the local study sites are responsible for:

- Obtaining local R&D and management approval (aided by the Trial Coordinating Centre)
- Provision of adequate clinic space and the identification of potentially eligible participants
- Conducting study procedures and follow-up according to study protocol
- Dealing with routine enquiries from participants and their families
- Obtaining appropriate information to confirm potential primary and secondary study endpoints
- Attend annual EVRA Study Collaborator Meetings to discuss study progress

11. DOCUMENT RETENTION

Data will be stored for a minimum of 10 years following completion of this trial. Data generated by this work will be processed in accordance with the Data Protection Act 1998.

12. PUBLICATION POLICY

The findings will be disseminated to General Practitioners, nursing staff, surgeons and other health care professionals at regular research and educational meetings organised at local, regional, national and international levels. All analyses will be performed in compliance with a predefined analysis plan. The chief investigator, clinical coordinators and trial coordinator will be responsible for drafting the main reports from the study. Draft copies of any manuscripts will be provided to local principal investigators at each local study site, TSC members and all other collaborators for review prior to publication. The results will be put forward for critical peer review with a view to publication in relevant medical and nursing journals.

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Appendix 1: Summary of assessments and follow-up visits

Time point	Estimated duration (mins)	Clinical evaluation[a]	Telephone follow-up[b]	Wound review / tracing	Wound photo	Venous duplex	Randomisation	Consent	Health Questionnaires (EQ-5D, SF-36, AVVQ)
Screening Visit	45	X				X		X*	
Baseline Visit	60-90	X		X	X		X	X**	X
1 month	30		X						
6 weeks	60-90	X		X?	X	X[c]			X
2 months	30		X	X?	X?				
3 months	30		X	X?	X?				
4 months	30		X	X?	X?				
5 months	30		X	X?	X?				
6 months	30		X	X?	X?				X
7 months	30		X	X?	X?				
8 months	30		X	X?	X?				
9 months	30		X	X?	X?				
10 months	30		X	X?	X?				
11 months	30		X	X?	X?				
12 months	30		X	X?	X?				X

a. Demographic details (age, sex, ethnicity), Pregnancy test for woman of child bearing potential. General clinical details (body mass index, ankle brachial pressure index – performed within previous 4 weeks, comorbidities, medication history). Ulcer details (duration, progression, previous ulcer history, size of current ulcer – using photography and planimetry). Details of venous disease (previous deep vein thrombosis, previous venous interventions, pattern of venous reflux on duplex)

b. . Ulcer healing assessment, compression type, AE assessment, Concomitant medications, health resource use

c. Only for those who have early endovenous treatment

*Approached **Taken

?dependant on whether the ulcer has healed tracing and photo will be taken at verification visit and taken weekly for 1 month. Once the ulcer has healed the patient will still be followed up with monthly phone calls.

EVRA (Early Venous Reflux Ablation) ulcer trial

A randomised clinical trial to compare early versus delayed endovenous treatment of superficial venous reflux in patients with chronic venous ulceration.

Version 5.0, 06/04/2017

MAIN SPONSOR: Imperial College London (Sponsor Number 13HH0722)

ISRCTN02335796

STUDY COORDINATION CENTRE: Imperial College Trials Unit

NRES reference: 13/SW/0199

IRAS Ref: 131153. UK CRN Study ID: 15078

		Date	Signature
Authorised by:	**Name:**	**11/05/2017**	
Professor Alun H Davies			

Revision History

Protocol Version	Date	Amendments
V5.0	06/04/2017	To incorporate the HTA funding extension to the trial to allow for the collection of longer term follow-up during October 2018 and March 2019 Amendments to the health economics section to clarify some items which were unclear in the previous version, and update the protocol to reflect new NIHR guidelines.
V4.0	16/03/2016	To correct sample size from 500 participants to 450 participants which was originally calculated erroneously To allow for a reduction in the number of photo verification visits performed if the core lab confirms the ulcer is healed.
V3.0	10/03/2014	Amended in order to display posters, leaflets and disseminate patient information sheets in primary care sites
V2.0	06/01/2014	A clearer definition of ulcer healing is required to clarify that healing cannot be assume if a scab is present. Statistics and Data Analysis' section amended for clarity of per-protocol analyses. Serious adverse event (section 8.2) amended for clarity. Section 5.4 amended to clarify that patients can be offered intervention in the standard care (compression arm) if their ulcer has not healed at 6 months.
V1.0	19/06/2013	N/A – Original Protocol

Study Management Group

Chief Investigator: Professor Alun H Davies

Co-investigators: Mr Manjit S Gohel, Mr Richard Bulbulia, Mr Keith R Poskitt, Professor Andrew Bradbury, Professor Nicky Cullum, Miss Sophie R Renton, Mr I Nyamekye

Statistician: Dr Jane Warwick

Health economist: Dr David Epstein

Study Management: Miss Francine M Heatley

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Miss Francine M Heatley

Address: Vascular Surgery Research Group, Room 4E3, 4th Floor East Wing

Charing Cross Hospital, Fulham Palace Road, London W6 8RF

Tel: 020 3311 7371

E-mail: f.heatley@imperial.ac.uk

Web address: www.evrastudy.org

Clinical Queries

Clinical queries should be directed to either the Local PI or the Study Coordinator who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office

Imperial College London and Imperial College Healthcare NHS Trust

Room 215, Level 2, Medical School Building

Norfolk Place

London, W2 1PG

Tel: 0207 594 1872

This protocol describes the EVRA study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, UK Clinical Trials Regulations, the Data Protection Act and other regulatory requirements as appropriate.

This project is funded by the National Institute for Health Research HTA (project number 11/129/197). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
ICTU	Imperial Clinical Trials Unit
REC	Research Ethics Committee
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee

1. INTRODUCTION

1.1 BACKGROUND

Chronic leg ulcers are open “sores” on the lower limbs situated between the ankles and knees, which fail to heal within 6 weeks. These ulcers represent a source of great discomfort and social isolation to patients who often complain of associated pain, odour and wound discharge. The time taken for the ulcers to heal means that the condition is also particularly frustrating to health carers involved in their management in hospital and community settings. 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[1]. 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[23]. 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[4]. It should also be noted that with an aging and increasingly obese population[5], the incidence and prevalence of venous ulceration are both likely to increase. Treatment of the condition in the UK produces a substantial cost burden estimated at £400-600 million per annum[6].

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 randomised trials are around 60-65%[78], and the true population healing rates are likely to be significantly lower. Some patients may never heal and those that do heal are at high risk of recurrent ulceration. These poor outcomes are likely to be a reflection of the severe underlying venous dysfunction in this patient group, although inadequate assessment and suboptimal treatment are also likely to be important contributing factors.

1.1.1 Pathophysiology of venous ulceration

The venous circulation of the lower limb has two components, the deep and superficial systems. Blood normally flows from the superficial to the deep veins and is prevented from flowing back down the leg under the influence of gravity by ‘one-way’ valves along the veins. When these valves become incompetent (leaky), the superficial veins usually become dilated and tortuous (varicose) and the resulting sustained high venous and capillary pressures lead to skin inflammation and ulceration (breakdown of skin). The deep veins also have valves, which may also become incompetent, but are not visible on the skin. Duplex ultrasound studies[91011] on patients in leg ulcer clinics suggest that:

- Around 50% of patients with venous leg ulcers have diseased superficial veins alone, with a further 30-40% having a mixture of superficial and deep venous disease. Both of these groups of patients benefit from correction of their

superficial venous reflux, which has been shown to reduce the risk of ulcer recurrence[12].

- A minority (5-10%) of patients with venous ulcers have diseased deep venous systems only, and are not amenable to surgical correction. These patients are usually treated with compression bandaging alone

Ulcer healing strategies are based on efforts to reduce this leakage (reflux) of blood back down the leg and into the skin, as this is considered the most significant cause of high venous pressure in most patients. Longstanding venous hypertension has been shown to cause a number of changes to the microcirculation in the lower leg, which can contribute to the chronic skin changes or eventual ulceration associated with chronic venous disease[13]. Compression bandaging to the leg (which may need to be re-applied 1-4 times per week) counteracts the gravitational force on the blood, in effect temporarily replacing the incompetent valves[14]. Diseased superficial veins can be surgically removed (open varicose vein surgery) or ablated using endovenous interventions (see below) without harming the overall venous function of the leg, theoretically removing a causative factor for recurrence of the ulcer after the compression bandaging has ceased. The deep vein defects are not generally amenable to surgery.

1.1.2 Treatment options for superficial venous reflux

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[15]. 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. Long-term studies have also identified significant complications of open surgery including nerve damage and recurrence of varicose veins, seen in over 60% of patients at 11 years in one randomised study[16].

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. Interventions such as ultrasound guided foam sclerotherapy (UGFS)[17], endovenous laser (EVLA)[18] or radiofrequency ablation (RFA)[19] can be performed using local anaesthesia in an outpatient setting. These treatments involve cannulation of the vein to be treated (usually under ultrasound guidance) and obliteration of the venous channel by either chemical ablation (using foam sclerosant), or thermal ablation (using a laser or radiofrequency fibre). Numerous randomised studies have demonstrated that endovenous modalities are, at worst, comparable to open surgery in terms of recurrence (and likely to be better), but clearly superior in terms of pain, bruising and other early complications[20-22]. Each of the different endovenous modalities has advantages and potential disadvantages, although all are less invasive than traditional open surgery. This is of particular relevance to patients with

chronic venous ulceration, who are often elderly, have extensive co-morbidities and may be reluctant to undergo surgical procedures involving general anaesthesia. Endovenous techniques can also be performed without discontinuing anti-coagulation therapy, which is increasingly prescribed in this patient population.

1.1.3 Summary of current research

The most significant study of superficial venous intervention in patients with venous ulceration is the ESCHAR study (Barwell, Poskitt; Lancet 2004 & Gohel, Poskitt; BMJ 2007)[712]. The study aimed to evaluate the role of traditional superficial venous surgery in reducing ulcer recurrence in patients with open or recently healed venous ulcers. Following prospective observational studies to inform power calculations, a total of 500 patients were randomised to compression therapy alone or compression with open surgery for superficial venous reflux. The group randomised to surgical treatment had significantly lower venous ulcer recurrence rates at 4 years (Figure 1).

Analysis stratified by pattern of venous reflux demonstrated that this clinical benefit was present for patients with isolated superficial venous reflux and patients with superficial and segmental deep reflux. This clearly indicated that the majority of patients with chronic venous ulceration could benefit from superficial venous intervention. As a result, the current optimal management of patients with venous ulceration includes the treatment of refluxing superficial veins to reduce the risk of ulcer recurrence[23].

Analysis of ulcer healing within the ESCHAR trial demonstrated that there was no significant improvement in ulcer healing rates for the group randomised to compression plus surgery (Figure 2). This finding has led many to conclude that treatment of venous reflux does not have a role in patients with open ulcers.

Figure 1. ESCHAR trial – ulcer recurrence

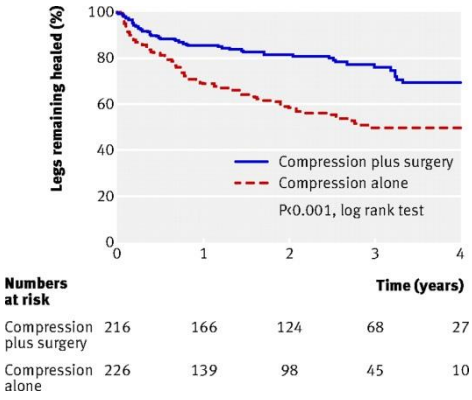
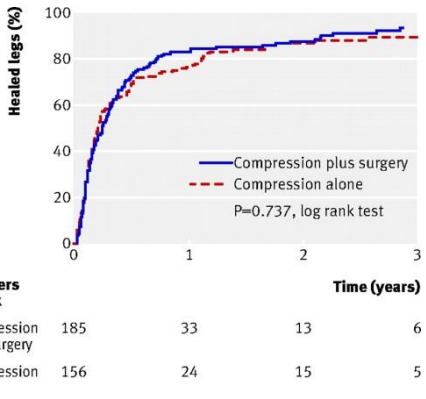


Figure 2. ESCHAR trial – ulcer healing



However, the ESCHAR study was designed and powered to assess ulcer recurrence rather than healing, and the statistical power of this trial was further weakened by a high cross-over rate, as around a quarter of patients randomised to surgery subsequently refused to have an operation. This highlights the need for a minimally invasive superficial venous treatment modality in this patient group. In addition, the

median time to treatment within the study was around 2 months, by which time smaller ulcers may have already healed with compression bandaging, and, in many cases, the surgical procedures used were suboptimal when judged by current standards. Consequently, it is plausible that the benefits of treating superficial venous reflux were underestimated in this study, particularly for the assessment of ulcer healing.

In a smaller Dutch randomised trial, 170 patients (200 legs) were randomised to compression alone or compression with surgical treatment of superficial reflux (including subfascial endoscopic perforator surgery – SEPS)[8]. Although results did not reach statistical significance, there was a clear trend towards improved ulcer healing rates and greater ulcer free time in the group randomised to surgery.

Despite the widespread acceptance of endovenous modalities, few prospective studies have been published reporting outcomes after endovenous treatment in patients with leg ulcers. In a prospective study of 186 patients with leg ulceration treated with UGFS, the ulcer healing rate was over 70% and the patient acceptability of treatment was excellent (Poskitt et al)[24]. In a further study of foam sclerotherapy in 130 patients, a healing rate of 82% was achieved (Bradbury et al)[25]. Whilst these small non-randomised studies lend support to our hypothesis that early intervention to correct superficial venous reflux will promote ulcer healing, a large randomised trial is required to provide reliable evidence and thus change practice.

1.2 RATIONALE FOR CURRENT STUDY

Whilst the management of patients with venous ulcers has evolved in recent years and ulcer healing and recurrence rates have shown some improvement, we believe that there is a strong argument in favour of this study at this time for the following reasons:

- The prevalence of venous ulceration is likely to increase, particularly with an aging and increasingly obese population. In view of the significant financial and psychosocial costs of venous ulceration, it is imperative that the optimal treatment strategies are identified.
- Despite numerous studies of topical ulcer treatments, the only treatment shown to improve venous ulcer healing is compression bandaging. Compression supports the venous circulation, but is poorly tolerated by some patients and does not address the underlying problem of venous reflux. The intervention in this proposal involves treating the underlying anatomical venous disorder using effective, minimally invasive endovenous interventions and offers a logical, deliverable and long-term approach to reducing venous hypertension.
- The treatment of superficial venous reflux has been transformed in recent years through the widespread use of minimally invasive, endovenous interventions, which patients find more acceptable than traditional open surgery.

- Ablation of superficial reflux should be considered in all patients with leg ulcers and superficial venous reflux, but if early intervention is associated with moderate improvements in ulcer healing compared to deferred intervention (i.e. post-healing), significant cost savings could be realised.
- Patients find venous leg ulcers painful, distressing and a significant inhibition to normal, independent life. Interventions to reduce the time to healing could reduce patient distress and significantly improve quality of life.

Therefore, we believe that there is a cogent argument for conducting this trial at this time. Non-randomised 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. The research team has a strong track record in relevant research areas and includes clinicians and researchers who successfully completed the landmark clinical trial on which this proposal is based (ESCHAR trial), and numerous other high impact clinical trials evaluating treatments in venous ulceration.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine 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.

2.2 SECONDARY OBJECTIVES

To investigate:

- The ulcer free time to 1 year and with the extension, up to 5 years (median of approximately 3.7 years)
- The technical success of endovenous interventions

3. PARTICIPANT ENTRY

3.1 PRE-REGISTRATION EVALUATIONS

Prior to commencing, information will be disseminated to GP practices in each recruiting region and meetings will be arranged with key community nursing staff and at leg ulcer clinics to promote the trial. Patients will be referred to secondary care as part of the standard care pathway as per the July 2013 NICE Guidelines. To aid recruitment, selected Primary Care trusts not currently involved in the trial will be set-up as Patient Identification Centres (PIC sites) displaying posters, leaflets and disseminating patient information sheets to patients. Selected Primary Care trusts involved in follow-up of the trial (research sites) will also aid recruitment by displaying posters, leaflets and disseminating patient information sheets to patients. Patients will still need to be referred to the secondary care recruiting sites to be consented and randomised into the trial.

At the referral visit patients will be given an appropriate time period to consider participation (at least 24 hours). Written consent will be obtained from those patients who agree to participate and randomization will be performed using the online service. For patients randomised to endovenous ablation of superficial venous reflux, a date for intervention will be booked as soon as possible (i.e. within 2 weeks). At each recruiting centre, an online log of all screened patients will be kept using the InForm system. Basic demographic data and reasons for non-eligibility will be recorded. Whilst participant baseline characteristics may vary slightly across recruiting sites, randomised treatment allocation will allow reliable assessment of the effects of early versus delayed endovenous ablation in ulcer healing.

3.2 INCLUSION CRITERIA

- Current leg ulceration of greater than 6 weeks, but less than 6 months duration
- Able to give informed consent to participate in the study after reading the patient information documentation
- Patient age > 18 years
- Ankle Brachial Pressure Index (ABPI) $\geq$ 0.8
- Superficial venous disease on colour duplex assessment deemed to be significant enough to warrant ablation by the treating clinician (either primary or recurrent venous reflux)

Patients who cannot speak / understand English will be eligible for inclusion and informed consent will be obtained with assistance from translation services as per standard clinical practice. In view of the lack of cross-cultural validation for quality of life tools, only healing outcome data will be collected.

3.3 EXCLUSION CRITERIA

- Presence of deep venous occlusive disease or other conditions precluding superficial venous intervention (at the discretion of local research team)

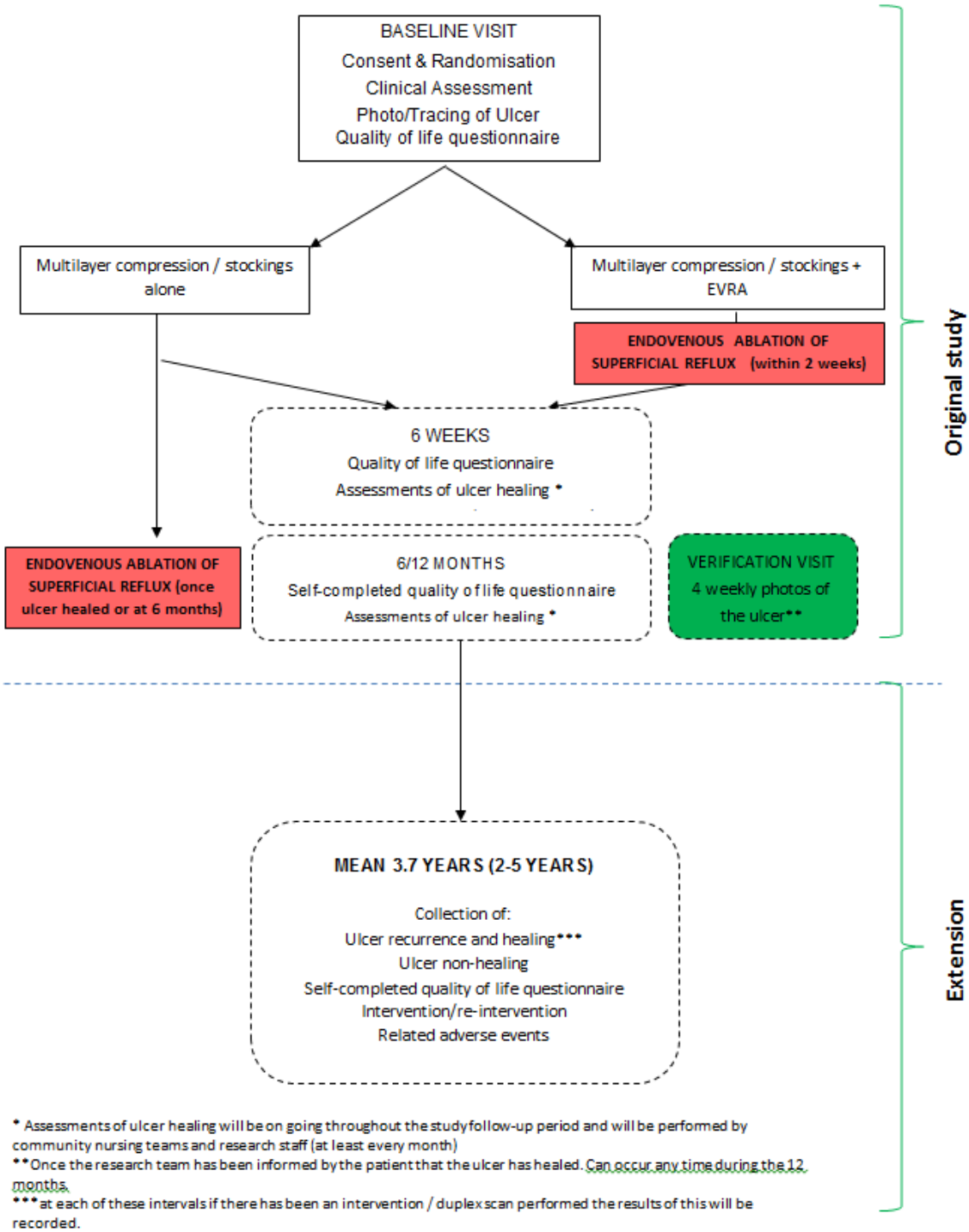
- Patients who are unable to tolerate any multilayer compression bandaging / stockings will be excluded. However, concordance with compression therapy can be variable for patients at different times. Patients who are generally compliant with compression, but unable to tolerate the bandages for short periods will still be eligible to inclusion. A period of non-compliance with compression bandages will not be considered a protocol violation, but a normal variation within the spectrum of ‘standard therapy’.
- Inability of the patient to receive prompt endovenous intervention by recruiting centre
- Pregnancy (female participants of reproductive age will be eligible for inclusion in the study, subject to a negative pregnancy test prior to randomisation)
- Leg ulcer of non-venous aetiology (as assessed by responsible clinician)
- If patient is deemed to require skin grafting they cannot be included

4. STUDY DESIGN

The EVRA ulcer trial is a pragmatic; multicentre randomised clinical trial with participants randomised1:1 to either:

1. 'Standard' therapy consisting of multilayer elastic compression bandaging/ stockings with deferred treatment of superficial reflux (usually once the ulcer has healed)
2. Early endovenous treatment of superficial venous reflux(within 2 weeks) in addition to standard therapy

The study design is summarised in Figure 3 below.



4.1 PATIENT RANDOMIZATION

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 – see 4.3.1). 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.

4.2 STUDY SETTING

Eligible patients with chronic venous ulcers will initially be recruited from the following centres:

1. Imperial College Healthcare NHS Trust (PI: Professor AH Davies)
2. Cambridge University Hospitals NHS Foundation Trust (PI: Mr MS Gohel)
3. Worcestershire Acute Hospitals NHS Trust (PI: Mr I Nyamekye)
4. North West London Hospitals NHS Trust (PI: Miss SR Renton)
5. Gloucestershire Hospitals NHS Foundation Trust (PI: Mr KR Poskitt)
6. Heart of England NHS Trust (PI: Professor A Bradbury)
7. University Hospital Birmingham NHS Trust (PI: Mr Rajiv Vohra)
8. City and Sandwell NHS Trust (PI: Miss Rachel Sam)
9. The Dudley Group NHS Trust (PI: Mr Andrew Garnham)
10. The Royal Wolverhampton Hospitals NHS Trust (PI: Mr Andrew Garnham)
11. York Hospitals NHS Foundation Trust
12. Hull & East Yorkshire Hospitals NHS Trust
13. The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
14. Frimley Park Hospital NHS Foundation Trust
15. Plymouth Hospitals NHS Trust

16. Bradford Teaching Hospitals NHS Foundation Trust
17. Salisbury NHS Foundation Trust
18. Leeds Teaching Hospitals NHS Trust
19. Sheffield Teaching Hospitals NHS Foundation Trust
20. Taunton and Somerset NHS Foundation Trust

As per section 3.1 Primary Care Trusts will be set-up as either PIC sites or research sites aiding recruitment by displaying posters, leaflets and disseminating patient information sheets. Patients will still need to be referred to the secondary care recruiting sites to be randomised into the trial.

4.3STUDY OUTCOME MEASURES

4.3.1 Primary outcome measure

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. Community or hospital healthcare staff, depending on the local model of care, will perform assessment of ulcer healing.

Data on the status of the reference leg will be collected throughout the study by research staff scrutinising community medical / nursing records and contacting the patient / community nursing teams by telephone(on a monthly basis at least).

If either the community nursing / medical staff or the patient believe that ulcer healing has been achieved, they will be asked to contact the local research centre immediately. This notification of possible ulcer healing will constitute a ‘trigger’ forth research staff at the recruiting centre to arrange an urgent verification assessment by a member of the healthcare team (within 1 week).

Verification will be by clinical assessment and digital photography, to be repeated weekly for 4 weeks, unless otherwise agreed by the trial manager. The digital images will be evaluated by two blinded expert assessors in order to ascertain the date of healing, which will be considered the primary healing end-point. For the purposes of the trial healing will be defined as the complete re-epithelialisation of the ulcerated (reference) leg in the absence of a scab (eschar) with no dressing required. Healing cannot be assumed if a scab present.

Disagreements will be resolved through discussion with involvement of a third blinded expert reviewer if necessary. This approach will be applied to patients in both treatment arms and is consistent with the methods utilized in other large HTA funded leg ulcer trials (e.g. VenUS IV). Legs deemed to have an open ulcer on clinical assessment would continue within the study. If healing is confirmed by clinical and

blinded photograph assessments at the first verification visit, the date of healing notification (by patient or community nurse) will be taken as the date of ulcer healing.

4.3.2 Secondary outcome measures

A number of secondary outcome measures will be evaluated in the EVRA study:

1. Ulcer Healing Rate: Healing rate will be reported at 24 weeks in addition to time to ulcer healing to allow comparison with other published studies.
2. Ulcer recurrence / Ulcer Free Time: Will be calculated up to 1 year for each study arm and with the extension, up to 5 years (median approximately 3.7 years). This will allow a very practical and easily understood assessment of the clinical difference between the 2 arms of the study. This will also allow comparison with other studies that have reported this outcome. In order to facilitate accurate calculation of reoccurrence / ulcer free time, clinical follow up will be continued after ulcer healing up to 1 year after randomisation.
3. 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, 12 months and at one time point between October 2018 and March 2019. The 6-week questionnaire will be given to the patient at the follow-up appointment, whereas other QoL questionnaires will be sent to the patient or completed by the patient via telephone. AVVQ is the most widely utilised disease specific QoL tool in venous disease and has been extensively validated. A score out of 100 points is calculated, with a higher score indicating more severe QoL impairment. Changes in QoL scores will offer a comparison with other studies and, in the standard treatment arm, will allow an assessment of the natural history of venous ulceration treated with compression.
4. Health Economic Assessment: A within-RCT cost effectiveness analysis will be carried out based on the data collected in the trial, Resource use items in hospital and community care related to the treatment of venous ulceration or complications will be recorded for each patient at each follow-up. Resource use will be multiplied by UK unit costs obtained from published literature, HRG costs, and manufacturers' list prices to calculate overall costs. A standard tariff will be applied for each bandage change. Utilities (QALYs) will be calculated from the EQ-5D questionnaire administered to patients at baseline, 6 weeks, 6 months, 12 months and at one time point between October 2018 and March 2019. The extent of missing data will be assessed and appropriate methods to handle missing data will be applied if necessary. The incremental cost-effectiveness ratio will be calculated and compared to current UK decision making thresholds. Discounting will be applied at the standard rate. Sensitivity analysis will be carried out to test the robustness of results to alternative assumptions (for example, about missing data, or using per-protocol estimates of treatment effect) or alternative data (for example, about unit costs). Probabilistic sensitivity analysis will be carried out using bootstrapping. A decision model will also be constructed to take account of

outcomes (such as recurrence or healing) that might occur beyond time horizon of the RCT, or to take account of other relevant comparators in this patient group.

5. Other Markers of Clinical Success: The Venous Clinical Severity Score (VCSS) 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 in the early arm.

4.4 DURATION OF FOLLOW-UP

In the original study, participants were to be followed-up until either:

1. 1 year post-randomization
2. Patient choice to withdraw from the study. Patients who no longer wish to complete quality of life questionnaires will be asked if they would object to the use of healing status data (to contribute to the primary outcome)
3. Death

In order to allow assessment of ulcer free time to 1 year, patients with healed ulcers were to be evaluated using telephone follow-up (performed by staff at the recruiting centre) on a monthly basis until 1 year. The aim of the telephone follow-up was to confirm that the ulcer remains healed, or in cases of ulcer recurrence, to ascertain the date of recurrence and of subsequent healing.

In December 2016 The HTA approved an extension to the trial follow-up allowing the collection of follow-up data for all patients who have not withdrawn consent to the trial. Data collection will commence in October 2018, allowing a median follow-up period of up to 5 years (median approximately 3.7 years) to be obtained (further details given in section 6.6).

4.5 STUDY DURATION

The EVRA study will take 70 months to complete. The revised study timetable is summarised in Figure 4.

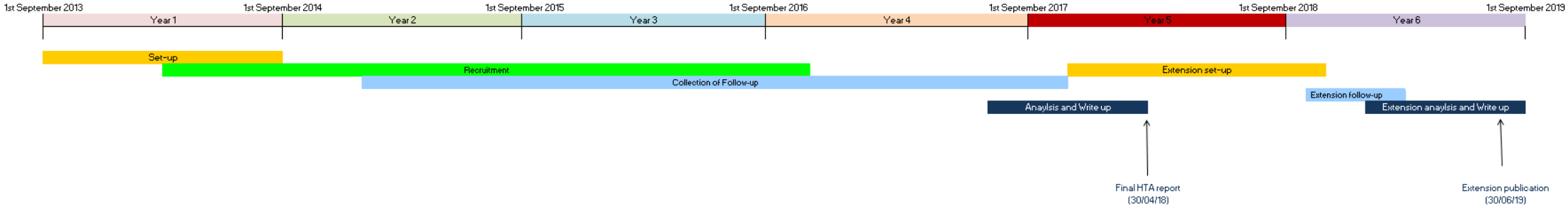


Figure 4. EVRA Study timeline

5. DETAILS OF INTERVENTIONS

5.1 VARIATIONS IN ENDOVENOUS INTERVENTIONS

A wide range of endovenous treatment modalities are now available and in widespread use for the ablation of superficial venous reflux. These include:

- Endovenous thermal ablation using laser or radiofrequency
- Ultrasound guided foam sclerotherapy (UGFS)
- Other endovenous interventions such as mechanochemical ablation, steam ablation and glue
- Any combination of the above treatments

In addition to the different modalities in use, the treatment strategy may also vary between institutions and between individual clinicians within the same department. Variations may occur in:

- Site of vein cannulation (and therefore the length of vein ablated)
- Location of treatment (‘office’ or clinic based versus operating theatre)
- Treatment strategy for sub-ulcer venous plexus (to ablate or not)
- The treatment of visible varicose veins (no treatment, UGFS or surgical avulsion) and the timing of any intervention

5.2 STANDARDISATION OF INTERVENTIONS IN EVRA STUDY

With the lack of consensus on a single, optimal endovenous treatment strategy for superficial reflux in patients with leg ulceration, perfect standardisation of interventions will be impossible. All endovenous interventions should be performed as deemed to be ‘optimal’ by the treating clinician for each individual patient, with the following stipulations:

1. The endovenous strategy must include ablation of the main truncal venous reflux
2. Truncal venous reflux should be treated to the lowest point of incompetence, where possible
3. Significant (as deemed by the treating clinician) residual / recurrent superficial reflux on the 6 week duplex scan, should be ablated
4. Patients should continue with multilayer compression / stockings immediately after treatment

5.3 STANDARDISATION OF COMPRESSION

Patients will receive the standard compression used in the individual centres prior to ulcer healing following randomisation (this will include four layer bandaging, three layer bandaging, European short stretch, stockings). Post healing the patients will be given compression hosiery in line with local policy.

5.4 FURTHER TREATMENT FOR STANDARD CARE (COMPRESSION ALONE) ARM

Patients randomised to multilayer compression / stockings alone can be offered endovenous treatment of superficial reflux once healing has been confirmed or at 6 month post randomisation (see 4.3.1). Endovenous ablation should be performed as per standard practice in the treating centre and details of this will be recorded. Endovenous intervention may also be offered if there is clinical deterioration in the active leg ulcer and it is clinically felt that the patient may benefit from early intervention. This will be recorded on the electronic case report form.

6. ASSESSMENT AND FOLLOW-UP

6.1 PATIENT IDENTIFICATION

Patients will be referred to secondary care for evaluation of the management of their leg ulcer as part of the standard pathway of care.

6.2 REFERRAL VISIT

At the initial visit the patient will be evaluated by clinical assessment and colour duplex examination, which is part of the normal investigation of a patient with leg ulceration. Dependant on the results of these tests, the patient will be asked if they would consider taking part in the trial and approached for consent. The patient will be given a minimum of 24 hours to consider the trial and if willing to participate will return to the leg ulcer clinic to give consent and undergo a baseline visit.

6.3 BASELINE VISIT

Patients will undergo detailed clinical assessment by the research nurse as part of the baseline evaluation (see *Appendix 1*). Recorded assessments will include:

- Demographic details (age, sex, ethnicity)
- Pregnancy test for woman of child bearing potential
- General clinical details (body mass index, ankle brachial pressure index – performed within previous 4 weeks, comorbidities, medication history)
- Ulcer details (duration, progression, previous ulcer history, size of current ulcer – using photography and planimetry)
- Details of venous disease (previous deep vein thrombosis, previous venous interventions, pattern of venous reflux on duplex)

Additional assessments will include:

- Assessment of Clinical, Etiologic, Anatomic, Pathophysiological (CEAP) score
- Assessment of venous clinical severity score (VCSS)
- Disease specific (Aberdeen varicose vein questionnaire – AVVQ) and generic (EuroQoL 5D – EQ5D & short form (SF) 36) quality of life assessments

At this visit, eligible and consenting patients will be randomised into the trial.

6.4 FOLLOW-UP ASSESSMENTS

Randomised patients will undergo routine leg ulcer care in community or hospital (or both) settings, in accordance with the local standard. This will equate to wound reviews and dressing changes ranging between once and 4 times per week (depending on the ulcer). The exact nature of dressings and date of dressing change will be documented by the completion of patient diaries. This will allow an accurate record of the dressing types used and will be collected and verified by the research nurse.

In addition, the following assessments will be conducted:

6.4.1 6-week clinic visit

- Clinical assessment
- In the compression plus early venous reflux ablation group, venous duplex scanning will be performed at 6 weeks post-randomization to verify anatomical treatment success. Depending on the results of the scan, the decision to perform further superficial venous interventions will be left to the discretion of the responsible clinical staff. Irrespective of the number and timing of venous interventions, all analyses will be performed on intention to treat.
- Wound tracing and photo
- Assessments of disease specific and generic quality of life (AVVQ, EQ5D & SF36) by means of self-completed questionnaire

6.4.2 Further follow-up

- Assessments of disease specific and generic quality of life (AVVQ, EQ5D & SF36) by means of self-completed questionnaire at 6 months and 12 months post-randomization (sent to the patient).
- The research team will perform monthly telephone evaluation of the patient and access the community notes or telephone the community nurses in order to collect and verify the data collected.
- Once the research team has been informed that the ulcer has healed the patient will undergo an urgent verification visit

6.5 URGENT VERIFICATION VISIT

- A member of the local research team will perform the four verification visits to confirm healing. Photographs will be taken and send to the Trials Unit for independent verification. In order to minimise inconvenience to the participants, once core labs confirms healing it is not necessary for the research team to perform further verification visits. Please note all four photos should be taken unless the trial manager confirms otherwise.

6.6 LONGER TERM FOLLOW-UP

For each randomised patient a single telephone assessment will be performed between October 2018 and 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)

The research teams will also evaluate healthcare records to:

- verify ulcer recurrence and healing events
- obtain specific details about venous investigations and interventions performed including delays to intervention.

No anatomical assessments of long-term treatment success are planned; however, additional treatments will be recorded and included in the health-economic evaluations.

7. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period in accordance with the Imperial College JCRO Archiving Study Documents SOP.

7.1 SAMPLE SIZE CALCULATION

The sample size calculation for this study was based on the primary outcome of ulcer healing. The ESCHAR trial was a similar randomised study, which published the final results in 2007 (see 1.1.3). A total of 500 patients with open or recently healed venous ulcers were randomised to standard therapy alone or standard therapy plus open surgery for superficial venous reflux. The study was powered and designed to evaluate differences in ulcer recurrence (rather than healing). Consequently, the median time from randomization to treatment delivery was over 7 weeks. Nevertheless, the 24-week healing rate in patients randomised to standard treatment (compression alone) was approximately 60%. Two recent prospective studies evaluating the early treatment of superficial venous reflux suggested that the 24-week healing rate may be as high as 82%[24 25].

In order to calculate a sample size for this study, a benefit associated with early treatment is estimated at around 15%. Assuming the 24-week healing rate in the standard arm is 60%, 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 in each arm, 254 healed leg ulcers in total). To incorporate further allowances for protocol violations and unexpected dropouts, the target sample size will be 450 patients.

Assuming a 15% drop out rate for the study and that 90% of primary ulcers eventually heal, it is estimated that >340 of the recruited 450 patients will be eligible for inclusion in the ulcer recurrence analysis. With this number of participants, and allowing for the healing rates (of the index ulcer prior to entry into this analysis of ulcer recurrence) to differ by up to 20% between the two study arms, the study extension will have at least 80% power to detect a difference of 15% or more in ulcer recurrence rates between the two arms at the 5% significance level.

7.2 PLANNED ANALYSES

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 member of the DMC only. Basic descriptive methods will be used to present the data on study participants, trial conduct, clinical outcomes and safety (in total and for each study group separately). The primary outcome will be time to complete healing. We will test the hypothesis that there is no difference in time to complete healing between the control and intervention groups using a log-rank test

(two-tailed, 5% significance level). Kaplan-Meier survival curves will also be presented and we will perform a subsidiary analysis investigating the effect of study centre, participant age, ulcer size and chronicity on time to complete healing using Cox regression. To adjust for potential surgeon and centre effects, surgeon and centre will be included in the Cox regression analysis as random effects. All analyses will be on an intention-to-treat basis. If there is substantial cross-over, per-protocol analyses may be explored for sensitivity analyses. Safety and tolerability data will be presented by the two arms on an intention-to-treat basis. The statistical analysis plan (SAP) for the original trial (follow up to 1 year) will be finalised prior to the final analysis. An additional SAP for the extension follow-up (up to 5 years) will be finalised before the analysis of extension data.

7.3 MISSING, UNUSED AND SPURIOUS DATA

There will be no data imputation for missing data in the primary endpoint (time to healing) and the secondary endpoint of ulcer free time. Any imputation methods used may be proposed for purposes of sensitivity analysis for other secondary outcomes, including ulcer healing rate, QoL and markers of clinical success. Imputation methods will be fully documented in the SAP.

7.4 DEVIATIONS FROM THE STATISTICAL ANALYSIS PLAN

Any deviation(s) from the final statistical analysis plan in the final analysis will be described and justification given in the final report.

7.5 HEALTH ECONOMIC ANALYSIS

The economic evaluation will be based on both a modelling exercise and a patient level in-trial analysis. The main analyses will be performed from the perspective of the NHS and Personal Social Services. Secondary analyses will be performed from a societal perspective. The price year will be 2017-18. Discounting will be applied according to UK Government guidelines. The study will be reported according to current guidelines for economic evaluation (CHEERS).

The within-trial analysis will compare early versus delayed endovenous treatment of superficial venous reflux in patients with chronic venous ulceration, within the time-horizon of the extended trial. Data will be collected by case note review and questionnaires completed at baseline, 6 weeks, 6 months,12 months and at a single time point during October 2018 and March 2019. Resource use items in hospital and community care related to the treatment of venous ulceration, adverse events or complications will be recorded for each patient at each follow-up. Resource use will be multiplied by UK unit costs obtained from published literature, Healthcare Resource Groups (HRG) costs, and manufacturers' list prices to calculate overall

costs. A standard tariff will be applied for each bandage change. Utilities (QALYs) will be calculated from the EQ-5D questionnaire administered to patients at each follow-up. The extent of missing data will be assessed and appropriate methods to handle missing data will be applied. The incremental cost-effectiveness ratio will be calculated and compared to current UK decision making thresholds. Sensitivity analysis will be carried out to test the robustness of results to alternative assumptions (for example, about missing data, or using per-protocol estimates of treatment effect) or alternative data (for example, about unit costs). Probabilistic sensitivity analysis will be carried out using bootstrapping.

A decision model will also be constructed to take into account outcomes that might be expected to occur beyond the timeframe of the RCT (e.g. recurrence, healing), the results of other RCTs that have assessed early or delayed endovascular therapy for treating venous ulcers, or any relevant comparators that are not considered in the RCT (e.g. surgery, bandaging only). The health states used in the model will be based on the natural history of chronic venous ulcers, to be obtained from the trial, from the literature and from expert opinion. . The inputs for the model will be the transition rates for moving from one state to another, the relative risks for each treatment compared with usual care, and the costs and HRQOL associated with each health state. Use of secondary and primary care patient resource use and EQ-5D responses associated with health states will be estimated mainly from the trial. Sensitivity analyses will be carried out to test the robustness of the model results to alternative assumptions and alternative data. Probabilistic sensitivity analysis will be carried out using Monte-Carlo simulation.

7.6 LOSSES TO FOLLOW-UP AND PROTOCOL VIOLATIONS

The primary assessment involves intention-to-treat analysis. Therefore, strenuous efforts will be made to ensure that only patients willing to undergo either immediate or delayed superficial venous ablation and compression bandaging are randomised. Monthly reports of protocol violations will be provided by local sites to the trial coordinators, who reserve the right to suspend or exclude sites in the event of wilful protocol violations. Similarly, efforts will be made to obtain complete follow-up for all randomised participants (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.

A high rate of protocol violation was seen in previous trials of venous ulceration (including the ESCHAR trial). This is likely to reflect the reluctance and apprehension of elderly patients to undergo surgical interventions involving general anaesthesia. The modern management 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, the rate of participation should be higher and rate of protocol violations 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.

8. ADVERSE EVENTS

8.1 REPORTING PROCEDURES

During the first 12 months all serious adverse events and all intervention-related adverse events should be reported. Any serious adverse events reported at the October 2018 to March 2019 follow-up time point should be reviewed the Principal Investigator to assess whether they are related to the treatment pathway and only related events should be reported to the sponsor via INFORM. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

8.2 RELATED ADVERSE EVENTS

Patients randomised to early venous intervention have the potential risks of treatment. Competent, experienced medical staff will perform all procedures and every effort will be made to prevent adverse effects. The adverse events listed below are expected to be related to the endovenous interventions used in the trial and should be reported. **Please note this is not an exhaustive list, if you suspect an event is related to treatment please contact the Trials Unit.**

Systemic

- **allergic reaction req. local / no treatment**
- **migraine**
- **visual disturbance**
- **fainting**
- **Cough / chest tightness**
- **Systemic infection**
- **PE**
- **TIA**
- **Stroke**

Local

- **Bleeding requiring intervention**
- **Blistering of skin**
- **Pressure damage**
- **Nerve damage**
- **DVT**
- **Hematoma**
- **Patient reported parathesia**
- **Pigmentation of skin**
- **Superficial thrombophlebitis**
- **New ulcer**
- **Deterioration of ulcer**
- **Wound infection**

8.3 NON SERIOUS ADVERSE EVENTS

All such events, which are judged by the local PI to be related to the interventions, whether expected or not, should be recorded in InForm

8.4 SERIOUS ADVERSE EVENTS

In addition to clinical assessments, patients will be contacted on a monthly basis by telephone for 12 months to identify any additional treatments, admissions or other complications related to their leg ulceration. Unrelated serious adverse events will also be recorded and reported in accordance with the Good Clinical Practice guidance up to 12 months. Serious adverse events (SAE) are defined as those adverse events that: result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; are cancer; or are other important medical events in the opinion of the responsible investigator (i.e. not life threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or more of the outcomes described previously).

All SAEs reported by participants at (or between) each follow-up visit will be recorded by local researchers and entered into InForm within 24 hours of the researcher becoming aware of the event.

All SAEs will be reported by the trial manager to the Sponsor and Chair of the Data Monitoring Committee. Related and unexpected SAEs will also be reported to the relevant Ethics Committee.

In the event that InForm is not accessible notify the Trial Manager, Francine Heatley:

Tel: 0203 311 7371 (Mon to Fri 09.00 – 17.00)

Email: EVRAtrial@imperial.ac.uk

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

After approval from the Research Ethics Committee, the study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Patients will not be specifically reconsented for the collection data in October 2018 as they already consented for the collection of longer term data at the outset. Patients will be asked, however at the telephone contact if they wish to continue in the study.

9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this study.

9.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.6 FUNDING

This project is funded by the National Institute for Health Research HTA (project number 11/129/197).

9.7 QUALITY ASSURANCE AND CONTROL

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition). Quality Control will be performed according to the requirements of the Risk Assessment performed by ICTU. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

10. STUDY MANAGEMENT

The study will be coordinated by a trial manager based at ICTU reporting to the Clinical Coordinators (MG and RB) and the Chief Investigator (AD). The Clinical Coordinators will liaise with local principal investigators (L-PI) to ensure that the trial is conducted locally according to protocol and in an expeditious manner. The organisational structure and responsibilities are outlines below.

10.1 PRINCIPAL INVESTIGATORS

The chief investigator and clinical coordinators have overall responsibility for:

- Design and conduct of the study
- Preparation of the Protocol and subsequent revisions
- Managing the Trial Coordinating Centre
- Development of SOPs

10.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established in line with HTA guidance, consisting of the chief Investigator, clinical coordinators, trial manager, trial statistician, patient representative, an independent chair and at least 1 other independent member will be formed and will meet on a 6-monthly basis to discuss trial progress. The TSC is responsible for:

- Agreement of the final Protocol
- Agreeing the Data Analysis Plan
- Reviewing progress of the study and, if necessary, agreeing changes to the Protocol
- Reviewing new studies that may be of relevance
- Review and approval of study reports

10.3 DATA MONITORING COMMITTEE

The independent Data Monitoring Committee (DMC) will be established in line with HTA guidance will focus on the rights, safety and wellbeing of study participants. DMC responsibilities are:

- Reviewing unblinded interim data according to the schedule agreed by all DMC members.
- Advising the Steering Committee if, in their view, the randomised data provide evidence that may warrant early termination for either safety or efficacy.

10.4 TRIAL COORDINATING CENTRE

The Trial Coordinating Centre (TCC) is responsible for the overall coordination of the Study, including:

- Study planning and organisation of Steering Committee meetings
- Agreement of each local recruitment plan
- Contractual issues with local study sites
- Ethics Committee applications
- Design, implementation and maintenance of IT systems for the study
- Auditing and monitoring of overall progress of the study
- Clinical safety monitoring (including the reporting of all “related” SAEs to the Chair of the DMC and Ethics Committee)
- Liaison with the Data Monitoring Committee and (where appropriate) with regulatory authorities and other outside agencies
- Responding to technical and administrative queries from local study sites

10.5 LOCAL STUDY SITES

The local principal investigators (L-PI) and clinical staff at the local study sites are responsible for:

- Obtaining local R&D and management approval (aided by the Trial Coordinating Centre)
- Provision of adequate clinic space and the identification of potentially eligible participants
- Conducting study procedures and follow-up according to study protocol
- Dealing with routine enquiries from participants and their families
- Obtaining appropriate information to confirm potential primary and secondary study endpoints
- Attend annual EVRA Study Collaborator Meetings to discuss study progress

11. DOCUMENT RETENTION

Data will be stored for a minimum of 10 years following completion of this trialin accordance with the Imperial College JCRO Archiving Study Documents SOP. Data generated by this work will be processed in accordance with the Data Protection Act 1998.

12. PUBLICATION POLICY

The findings will be disseminated to General Practitioners, nursing staff, surgeons and other health care professionals at regular research and educational meetings organised at local, regional, national and international levels. All analyses will be performed in compliance with a predefined analysis plan. The chief investigator, clinical coordinators and trial coordinator will be responsible for drafting the main reports from the study. Draft copies of any manuscripts will be provided to local principal investigators at each local study site, TSC members and all other collaborators for review prior to publication. The results will be put forward for critical peer review with a view to publication in relevant medical and nursing journals.

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Appendix 1: Summary of assessments and follow-up visits

Time point	Estimated duration (mins)	Clinical evaluation*	Telephone follow-up**	Wound review/photo /tracing***	Collection of further endovenous intervention / duplex report	Venous duplex	Randomisation	Consent	Health Questionnaires (EQ-5D, SF-36, AVVQ)
Screening Visit	45	X				X		X[a]	
Baseline Visit	60-90	X		X***			X	X[b]	X
1 month	30		X						
6 weeks	60-90	X		X?***		X[c]			X
2 months	30		X	X?					
3 months	30		X	X?					
4 months	30		X	X?					
5 months	30		X	X?					
6 months	30		X	X?					X
7 months	30		X	X?					
8 months	30		X	X?					
9 months	30		X	X?					
10 months	30		X	X?					
11 months	30		X	X?					
12 months	30		X	X?					X
Extension follow-up Oct18 to Mar 19	240	X[d]	X		X			X[e]	X

*. Demographic details (age, sex, ethnicity), Pregnancy test for woman of child bearing potential. General clinical details (body mass index, ankle brachial pressure index – performed within previous 4 weeks, comorbidities, medication history). Ulcer details (duration, progression, previous ulcer history, size of current ulcer – using photography and planimetry). Details of venous disease (previous deep vein thrombosis, previous venous interventions, pattern of venous reflux on duplex)

**. Ulcer healing assessment, compression type, AE assessment, Concomitant medications, health resource use. ***tracing only performed at baseline & 6 weeks

a. Approached b Taken c. Only for those who have early endovenous treatment d. review of clinical notes only e. patients will not be reconsented as already consented for longer term follow-up at outset but will be asked if they wish to continue

?dependant on whether the ulcer has healed photo will be taken at verification visit and taken weekly for 4 weeks, unless otherwise confirmed by the trial manager. Once the ulcer has healed the patient will still be followed up with monthly phone calls.

Protocol – Summary of changes

Version	Date	Approved by ethics	List of changes
1.0	19/06/2013	15/08/2013	*N/A original protocol*
2.0	06/01/2014	29/01/2014	1. Addition of abbreviation table, the sponsor, IRAS and UKCRN numbers 2. 'randomized' replaced with English spelling 'randomised' throughout the document 3. Study setting (section 4.2, page 12) amended to clarify that additional centres may join the trial at a later date 4. Definition of ulcer healing clarified (Page 13), 'For the purposes of the trial healing will be defined as the complete re-epithelialisation of the ulcerated leg in the absence of a scab with no dressing required. Healing cannot be assumed if a scab present.' 5. 4.3.2 Secondary outcome measures section amended to include 'ulcer reoccurrence'. 6. 'Assessment of range of ankle movement' removed from the baseline assessment section (Page 17) 7. Section 5.4 amended to clarify that patients can be offered intervention in the standard care (compression arm) if their ulcer has not healed at 6 months. 8. Statistics and Data Analysis (section 7, Page 20) amended to reference Imperial College JCRO Archiving Policy 9. Statistics and Data Analysis', sample size paragraph (section 7.1, Page 20) amended for clarity, planned analysis paragraph (section 7.2, Page 20) amended for clarity of per-protocol analyses. 10. Statistics and Data Analysis' section (Page 21). Addition of sections 7.3 Missing, Unused and Spurious Data & 7.4 Deviations from the statistical analysis plan added 11. Statistics and Data Analysis' section. Interim analyses: role of the Data Monitoring Committee (Page 22) removed / simplified into Section 10.3 to refer to the DMC charter. Interim analyses are now fully described in section 7.2 and the role of the DMC in section 10.3. 12. Amend all multilayer bandage compression to multilayer bandage compression / stockings 13. Serious adverse event (section 8.2) amended to clarify that SAEs should be reported to the Trial Manager by entering the data into InForm within 24 hours of becoming aware of the event. 14. Section also amended to confirm that all SAEs will be reported to the sponsor and DMC but only related, unexpected SAEs will be reported to the ethics committee. 15. Serious adverse event (section 8.2) amended to list all the expected adverse reactions
3.0	10/03/2014	24/03/2014	1. Section 3.1 (Page 10) amended to add 'Patients will be referred to secondary care as part of the standard care pathway as per the July 2013 NICE Guidelines. To aid recruitment, selected Primary Care trusts not currently involved in the trial will be set-up as Patient Identification Centres (PIC sites)

			displaying posters, leaflets and disseminating patient information sheets to patients. Selected Primary Care trusts involved in follow-up of the trial (research sites) will also aid recruitment by displaying posters, leaflets and disseminating patient information sheets to patients. Patients will still need to be referred to the secondary care recruiting sites to be consented and randomised into the trial.' 2. Section 4.2 Study Setting (Page 14) amended to add 'As per section 3.1 Primary Care Trusts will be set-up as either PIC sites or research sites aiding recruitment by displaying posters, leaflets and disseminating patient information sheets. Patients will still need to be referred to the secondary care recruiting sites to be consented and randomised into the trial. ' 3. Section 4.2 Study Setting (Page 14) amended to add the additional secondary care sites who will recruit into the study.
4.0	16/03/2016	12/04/2016	1. 7.1 SAMPLE SIZE CALCULATION amended to state '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 in each arm, 254 healed leg ulcers in total).' 'To incorporate further allowances for protocol violations and unexpected dropouts, the target sample size will be 450 patients.' This was to correct the original sample size of 500 participants which was calculated in error to the correct value of 450.
5.0	06/04/2017	24/05/2017	1. To incorporate the HTA funding extension to the trial to allow for the collection of longer term follow-up during October 2018 and March 2019. 2. Amendments to the health economics section to clarify some items which were unclear in the previous version, and updates the protocol to reflect new NIHR guidelines.

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

Chief Investigator: Professor Alun H Davies

EVRA

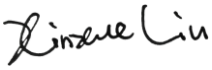
ISRCTN:	ISRCTN02335796
NRES Ref:	13/SW/0199
SAP Version:	Version 2
Date:	08th April, 2016

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

This statistical analysis plan is based on protocol version 3.0 [10/03/2014]

Approvals

This SAP is approved by:

Version	Name	Role	Signature	Date
2.0	Professor Alun H Davies	Chief Investigator		08/04/2016
	Dr Jane Warwick	Senior Statistician		11/04/2016
	Dr Xinxue Liu	Trial Statistician		08.04.2016

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.

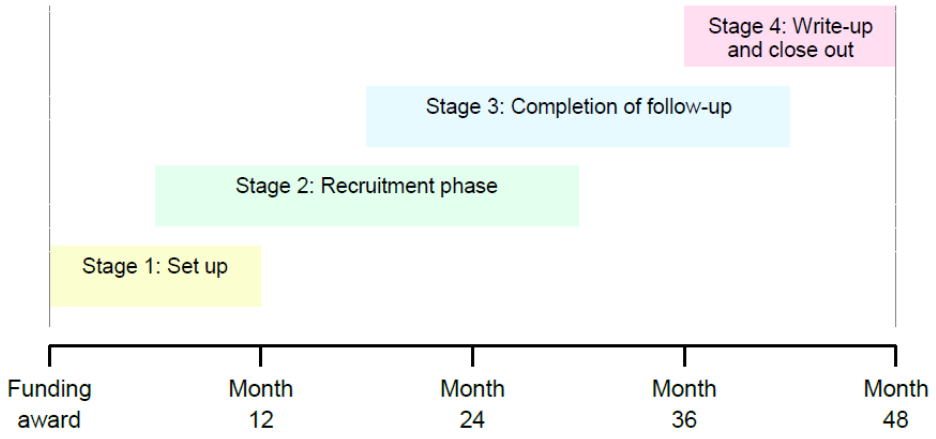


Figure 1 EVRA study Gantt chart

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 will be 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 log-rank test with stratification by study centre (two-tailed, 5% significance level). Kaplan-Meier survival curves will also be presented and as a subsidiary analysis we will investigate the effect of participant age, ulcer size at baseline and chronicity on time to complete healing using Cox regression with centre included in the model as random effect to adjust for potential centre effect.

For the secondary outcome of ulcer free time, multiple regression will be used adjusting 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.

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 1).

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 Primary Endpoints

The primary outcome will be 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 log-rank test with stratification by study centres. Kaplan-Meier survival curves will also be presented. We will investigate the effect of the study intervention on time to complete healing after adjusting for potential confounders listed in section **2.1** using Cox regression. To adjust for potential centre effect, centre will be included in the Cox regression analysis as random effect (Table 9).

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

Table 5 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. We will investigate the effect of the study intervention on ulcer free time after adjusting for potential confounders (Table 9) using multiple linear regression (if the assumption of normality can be met). If the assumption of normality cannot be met (there is no suitable transformation), ulcer free time will be categorized and analysed using appropriate regression methods to adjust for

potential confounders. The 24-week healing rate and associated 95% confidence interval will be obtained from the Kaplan-Meier analysis (4.3).

4.5 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. Depending on the distribution of the data, the means and 95% CI of means or medians and inter-quartiles at each time point, including baseline, 6-week, 6-month and 12-month after randomisation, will be reported.

4.6 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 6 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.

4.7 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 7 and Table 8). 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.

4.8 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. 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 (pentoxyfilne)		
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		
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 Summary of 24-week ulcer healing rate and ulcer free time*

	EVRA	Standard
	N=	N=
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 6 Summary of clinical success at 6 weeks after randomisation

	EVRA	Standard	P
	N=	N=	
VCSS total score			
Clinical classification downgrade from C6 to C5			
Yes			
No			

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

Table 7 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 8 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*

Table 9 Summary of the results

	Univariate model*		**Multivariate model†**	
	Effect of EVAR compared to Standard	P value	Effect of EVAR compared to Standard	P value
Time to ulcer healing				
Ulcer free time				

* *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).*

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.

2. Pang KH, Bate GR, Darvall KA, Adam DJ, Bradbury AW. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. Eur J Vasc Endovasc Surg 2010;40(6):790-5.

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.

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

Chief Investigator: Professor Alun H Davies

EVRA

ISRCTN:	ISRCTN02335796
NRES Ref:	13/SW/0199
SAP Version:	Version 4
Date:	26th October 2017

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

This statistical analysis plan is based on protocol version 5.0 [11/05/2017]

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.
	Dr Xinxue Liu	Trial Statistician		09/11/2017
	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.

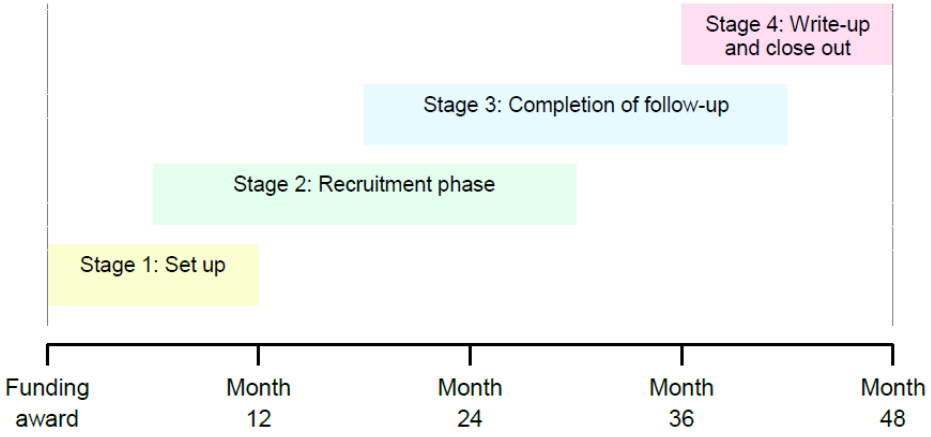


Figure 1 EVRA study Gantt chart

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.

2. Pang KH, Bate GR, Darvall KA, Adam DJ, Bradbury AW. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. Eur J Vasc Endovasc Surg 2010;40(6):790-5.

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.

Statistical analysis plan (SAP) – Summary of changes

Version	Date	Reviewers	Draft or Signed	List of changes
1.0	15/10/2014	Senior statistician	Draft	*N/A draft only*
2.0	08/04/2016	Internal study Team, TSC	Signed by senior statistician and trial statistician	*First effective version* 1. To update the sample size correction; 2. To remove the adjustment of surgeon as a random effect in all regression analysis as the data is not collected; 3. To clarify the definition of ulcer-free time to 1 year and the analysis plan for ulcer free time; 4. To clarify the analysis plan for 24-week healing rate; 5. To clarify how to derive time to ulcer healing for censored patients; 6. To add per-protocol analysis.
3.0	02/06/2016	Internal study Team	Signed by CI and trial statistician	1. To update the protocol version number to 4.0 as the new protocol was approved.
4.0	26/10/2017	Internal study Team, TSC	Signed by CI, senior statistician, trial statistician, and TSC chair	1. To include TSC chair's signature as a results of trial unit SOP update; 2. To update the protocol version number to 5.0 as the new protocol was approved; 3. To change the primary outcome analysis from study centre-stratified log-rank test to univariate Cox regression adjusting for study centre as random effect, so that the treatment effect can be quantified; 4. The clarify the population for analysis; 5. To include the summary of interventional treatment; 6. To define the subgroup analysis; 7. To clarify the methods to check cox regression model assumption; 8. To clarify the analysis method for QoL data.

Summary of SAP deviations:

1. The sensitivity analysis of ulcer free time to 1-year in all the patients was not performed as this would be biased (see pages 8-9 of SAP V4.0)
2. The analysis method for quality of life data was amended from a variable to mix-model analysis as a mix-model is more appropriate for time-series data.