NIHR HTA Programme

26 September 2013

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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.

Version 1.0 19/06/2013

MAIN SPONSOR: Imperial College London

FUNDERS: NIHR HTA

STUDY COORDINATION CENTRE: Imperial College Trials Unit

NRES reference: 13/SW/0199

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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:

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Funder NIHR – HTA Rapid Trials grant

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

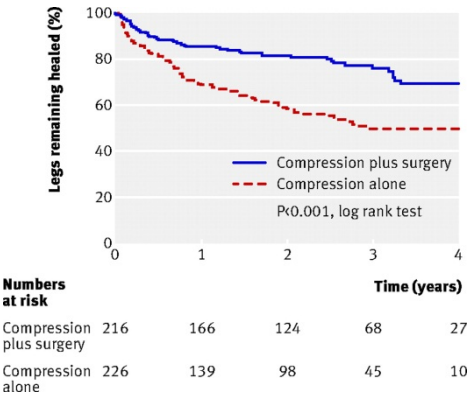
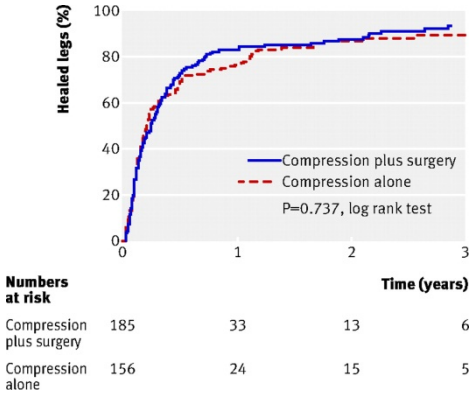


Figure 2. ESCHAR trial – ulcer healing



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’.

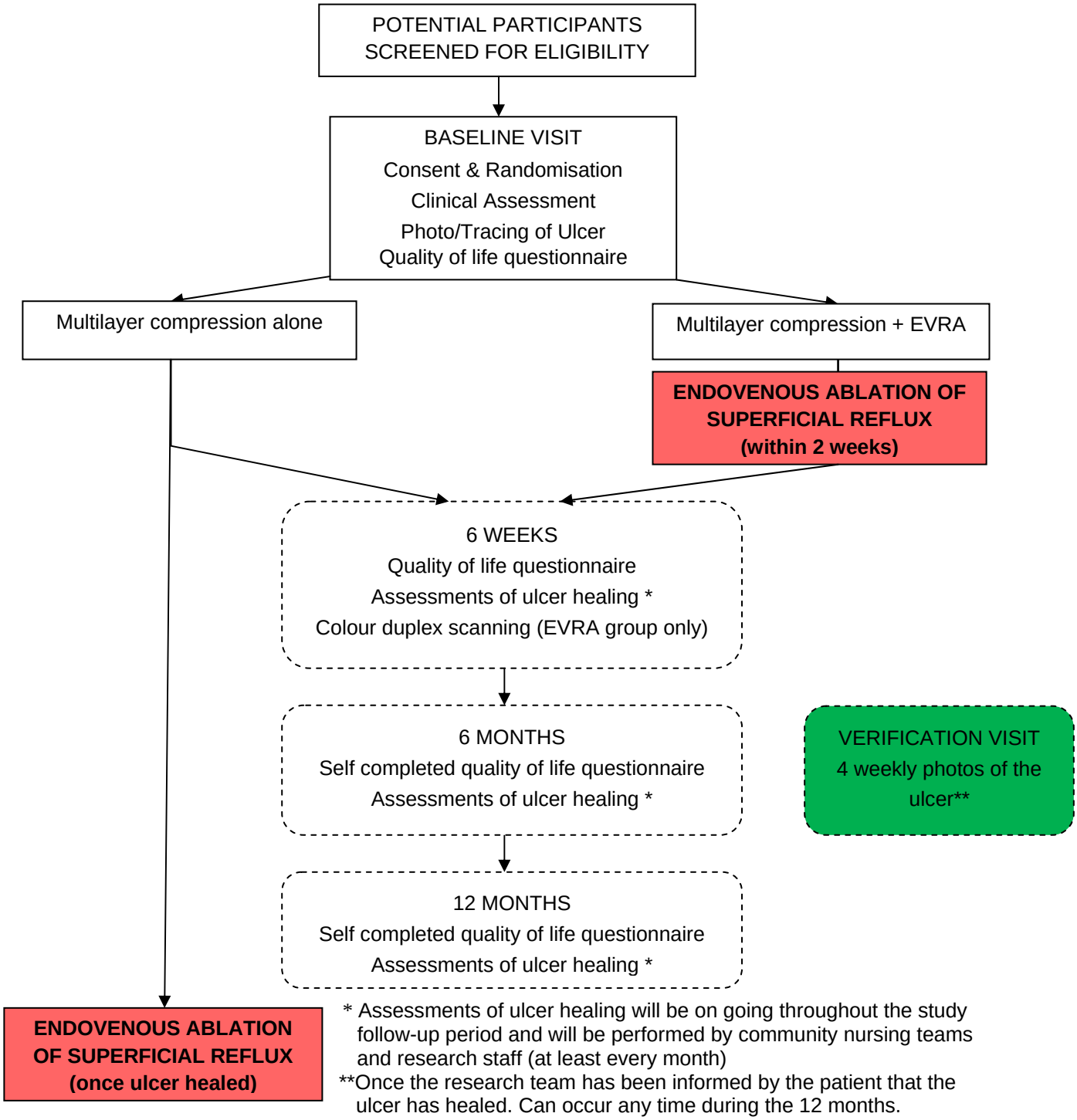
- Inability of the patient to receive prompt endovenous intervention by recruiting centre
- Pregnancy (female participants of reproductive age will be eligible for inclusion in the study, subject to a negative pregnancy test prior to randomisation)
- Leg ulcer of non-venous aetiology (as assessed by 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.

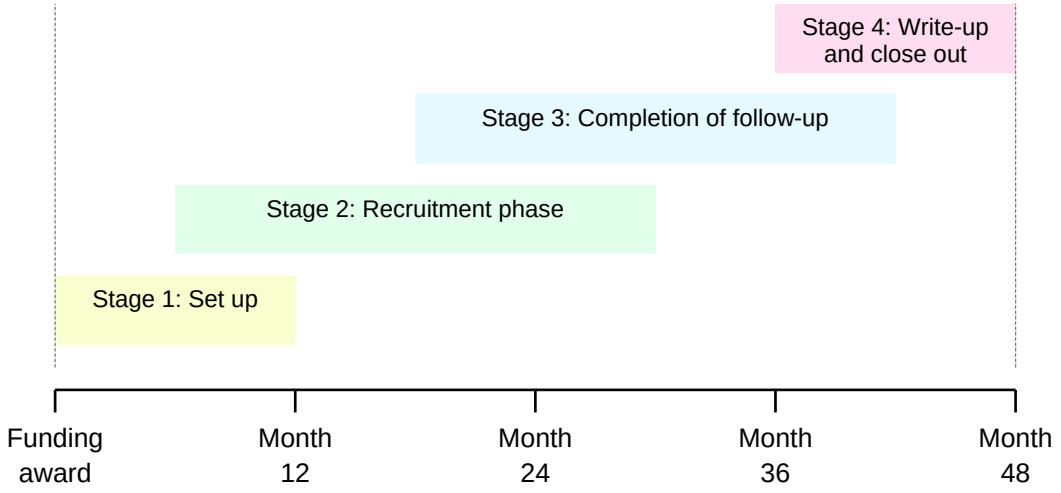


Figure 4. EVRA study Gantt chart

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: xxx, attention xxx

Please send SAE forms to: xxx

Tel: xxx (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			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

*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.