

# **NIHR HTA Programme**

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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**The CLASS Trial**  
**Comparison of LAser, Surgery and foam Sclerotherapy**

**Research Protocol**

Randomised controlled trial comparing foam sclerotherapy, alone or in combination with endovenous laser therapy, with conventional surgery as a treatment for varicose veins.

## **1. Project title**

Randomised controlled trial comparing foam sclerotherapy, alone or in combination with endovenous laser therapy, with conventional surgery as a treatment for varicose veins.

## **2. Background**

### *2.1 The burden of the problem*

The treatment of patients with varicose veins results in a considerable workload and financial burden to the NHS. Visible varicose veins occur in up to 40% of men and 32% of women, resulting in approximately 95,000 operations being performed each year in England alone<sup>1,2</sup>, approximately 20% of these operations are for recurrent varicose veins<sup>3</sup>. Throughout the United Kingdom there are considerable variations in access to treatment for uncomplicated varicose veins as it may be believed to be a cosmetic procedure<sup>4</sup>. The evidence to support this belief is mixed<sup>5-9</sup> and a recent randomised controlled trial of surgery versus conservative management of patients with uncomplicated varicose veins estimated that the incremental cost per QALY gained was £4682, with a 70 percent probability that the cost per QALY would be less than NICE's threshold of £20,000<sup>10</sup>.

### *2.2 Current treatment options*

The mainstay of treatment for incompetent varicose veins is surgery in the form of saphenofemoral junction ligation or short saphenous ligation, stripping and multiple phlebectomies of non-trunk varicosities. Current evidence suggests a recurrence rate for conventional surgery at 5 years of 32% for long saphenous and 50% for short saphenous veins<sup>3</sup>. Recently, foam sclerotherapy and endovenous laser ablation (EVLA) have emerged as possible alternative minimally invasive local anaesthetic treatment options. Another technique - the percutaneous introduction of radiofrequency probes to ablate the long saphenous veins - is also available but is more costly and is less suited for local anaesthesia due to the contact time required between the probe and vein endothelium. As such it will not be considered further in this application. EVLA and foam sclerotherapy aim to reduce the surgical trauma, bruising, scarring and time off work associated with conventional surgery. Based on reviews conducted by our group in the Health Services Research Unit, NICE has published Interventional Procedures guidance on both these procedures, stating there is adequate evidence on their safety and efficacy for use in the NHS<sup>11</sup> [<http://www.nice.org.uk>].

Despite uncertainty about clinical and cost effectiveness, use of foam sclerotherapy and EVLA is increasing in the UK as alternatives to conventional surgery. These interventions have the potential to increase throughput of varicose vein patients without the need for expensive operating facilities. However, this benefit appears to be offset by the need for the patient to return for further treatment. There are currently only two completed randomised controlled trials of limited follow-up (referred to in detail below). Critics of the procedures point to the unknown effect of not treating tributaries at the sapheno-popliteal and saphenofemoral junction and the need for several treatment sessions compared to "one-stop" surgery. The current evidence for foam sclerotherapy and EVLA is summarised below.

### Foam sclerotherapy

Foam sclerotherapy induces irritation of the endothelium leading to thrombosis. Current use of foam sclerotherapy is off-licence, and can use several different liquid sclerosants of varying concentrations. These are mixed with air to produce foam. The use of foam rather than a liquid increases the contact with the endothelium, with less dilution by mixing with venous blood but the foam may vary in consistency, which may effect efficacy<sup>12</sup>.

A recent systematic review undertaken by our Group in the Health Service Research Unit of the safety and efficacy of foam found that foam appears efficacious in terms of obliterating the main trunk veins<sup>13</sup> but more than one treatment session may be required to obtain obliteration of the main truncal vein. In a series of 500 patients, Cabrera achieved obliteration of the long saphenous

vein in 81% of cases: 86% of patients achieved this after one injection, while 11% required two injections and 4% required a third<sup>14</sup>. Across studies included in the review, the median rate of recurrence or development of new varicose veins ranged from 10 to 28% but the risk of recurrence or development of new veins was not significantly different to that of comparator treatments<sup>13</sup>. To date there has only been one randomised controlled trial of foam sclerotherapy compared with either liquid sclerotherapy or conventional surgery (ligation and stripping of the long saphenous vein) involving 272 patients. Foam sclerotherapy was found to be less effective in terms of the obliteration of the long saphenous vein compared to surgery at follow-up ranging from 1 month to 1 year (120/178 (68%) compared with 81/94 (86%), respectively)<sup>15</sup>. Following foam sclerotherapy, patients required a median of two days to return to normal activity compared with 13 days following surgery. Compared with liquid sclerotherapy or surgery, there was no evidence of differences in patient satisfaction, disappearance of varicosities or change of disease-specific quality of life as measured by the Aberdeen Vein Questionnaire and the CEAP score (a widely accepted measure of venous dysfunction). No RCTs were identified comparing foam sclerotherapy with EVLA. In summary, the systematic review highlights that there is insufficient evidence to reliably compare the effectiveness of foam sclerotherapy with other minimally invasive therapies or surgery.

The main safety concern regarding foam sclerotherapy is the potential for the foam to enter the deep venous system. As a result, the NICE guidance for foam sclerotherapy recommends special arrangements for consent, audit and research. Also limits have been recommended on the amount of foam injected per session<sup>16</sup>, necessitating additional treatment sessions to deal with non-truncal varicosities. In the recent systematic review<sup>13</sup> the incidence of deep venous thrombosis varied from 0.3 to 3%, transient visual disturbance occurred in up to 2.8%, transient ischaemic attack in 0 to 0.3% of cases, and there has been one reported ischaemic stroke occurring immediately after injection with partial recovery at three months. This occurred in a patient with a patent foramen ovale, which is present in 25% of the population. Other potential adverse events include thrombophlebitis (15-58%), early pigmentation (11-50%), skin necrosis (0.01-0.9%), ulceration (0-7%) and allergy (0.3%). Published data indicate that 43% of patients undergoing foam sclerotherapy require a single treatment session, with an additional 48% requiring 2 sessions<sup>17</sup>.

#### Endovenous laser ablation (EVLA).

Most studies describing EVLA use have used either 810nm or 940nm diode lasers based upon a haemoglobin absorption peak to red/infrared light of 800-1000 nm. The heat generated by the laser was believed to result in thermal damage to the endothelium and sub-endothelial layer resulting in focal coagulative necrosis and shrinkage leading to thrombotic occlusion of the vein<sup>18</sup>. However, histological studies at 3 and 6 months following EVLA indicate failure of endothelial regeneration and progressive damage to the muscle layers of the vein wall resulting in further shrinkage and occlusion<sup>19</sup>. Studies have shown that between 30% and 99% of patients undertaking EVLA require secondary treatment using foam sclerotherapy for non-trunk varicosities<sup>20</sup>.

Recently it has been shown that successful occlusion is dependent on the energy used and was achieved in all veins treated with greater than or equal to 60 joules/cm<sup>4</sup>. The presence of patent groin tributaries post EVLA does not appear to have an impact on clinical outcome at 12 months follow-up<sup>21</sup>. A randomised controlled trial of EVLA versus surgery, which has been performed by Gough and colleagues, is due to report in the near future (submitted to BJS). To date 102 limbs have been randomised to EVLA (n=64) or surgery (n=39). At 3 months follow-up, abolition of reflux was achieved in 98% EVLA and 92% of surgical patients, EVLA patients had a quicker return to normal activity and work (p=0.01).

A recent systematic review<sup>22</sup> assessed the effectiveness and safety of EVLA in 13 case series involving 1289 patients (1631 limbs) with duplex proven primary venous reflux. EVLA was effective in the short term, with occlusion of the long saphenous vein occurring in 88-100% of limbs. Mundy and colleagues concluded that EVLA appeared to be safe, although there were two

reported cases of incorrect positioning of the laser within the deep venous system (which produced no long-term complications) and one reported deep venous thrombosis. Other complications reported were: superficial laser burns reported in 4.8% of patients in one study which used a very high laser energy, ecchymosis or skin discoloration (23-100%) which was generally self limiting, phlebitis in 1.6% of limbs, and saphenous paraesthesia in 1-36.5% of limbs<sup>22</sup>. The Australian Medical Services Advisory Committee in its 2003 assessment report concluded that EVLA and conventional surgery were comparable in terms of safety<sup>23</sup> (<http://www.msac.gov.au>).

Our rationale for including EVLA in addition to foam sclerotherapy in this proposed randomised controlled trial is five-fold:

- 1) As indicated above, foam sclerotherapy of non-trunk varicosities is part of the EVLA 'package'. A comprehensive assessment of the use of foam sclerotherapy in the NHS should therefore include this EVLA package as a randomised arm.
- 2) Whilst EVLA is considered comparable to surgery in terms of safety, concerns have been raised by NICE regarding the safety of foam sclerotherapy, especially for truncal veins because of the risk of foam entering the deep venous system. The risk of non-trunk sclerotherapy with EVLA is unknown and needs establishing; if the safety concerns regarding foam sclerotherapy are substantiated in truncal veins, the EVLA package might be the only viable novel alternative to conventional surgery.
- 3) Although the literature supports the short-term efficacy of EVLA as an effective alternative to conventional surgery, long-term data are lacking;
- 4) The inclusion of two minimally invasive treatments in this study may facilitate recruitment and determine which of the two is the most effective in the medium/long term; and
- 5) The use of both foam sclerotherapy and EVLA are increasing in the UK, based on personal preferences and patient demand. A 2005 survey by one of the applicants reported that 9% and 5% of consultants respectively using foam sclerotherapy and EVLA<sup>24</sup>. A survey of members of the Vascular Surgical Society of Great Britain and Ireland and the Venous Forum of the Royal Society of Medicine during June 2006 (Winterborn, personal communication) revealed that the vast majority of surgeons (96%) offered conventional surgery to NHS patients. Ninety five surgeons (27%) offered foam sclerotherapy, 66 surgeons (19%) offered EVLA and only 12 (3%) offered radiofrequency ablation. The non surgical modalities were more frequently offered in surgeon's private practice.

### 3. Objectives

Primary objective: To compare the clinical and cost-effectiveness of conventional surgery with two minimally invasive treatment modalities (a) foam sclerotherapy alone of main long or short saphenous trunk and non-trunk varicosities and (b) Endovenous laser ablation (EVLA) of main trunk including foam sclerotherapy of non-trunk varicosities performed under local anaesthetic in respect of quality of life for each intervention at 6 months (and ultimately through to 5 years) and cost-effectiveness as cost per quality adjusted life year (QALY) gained.

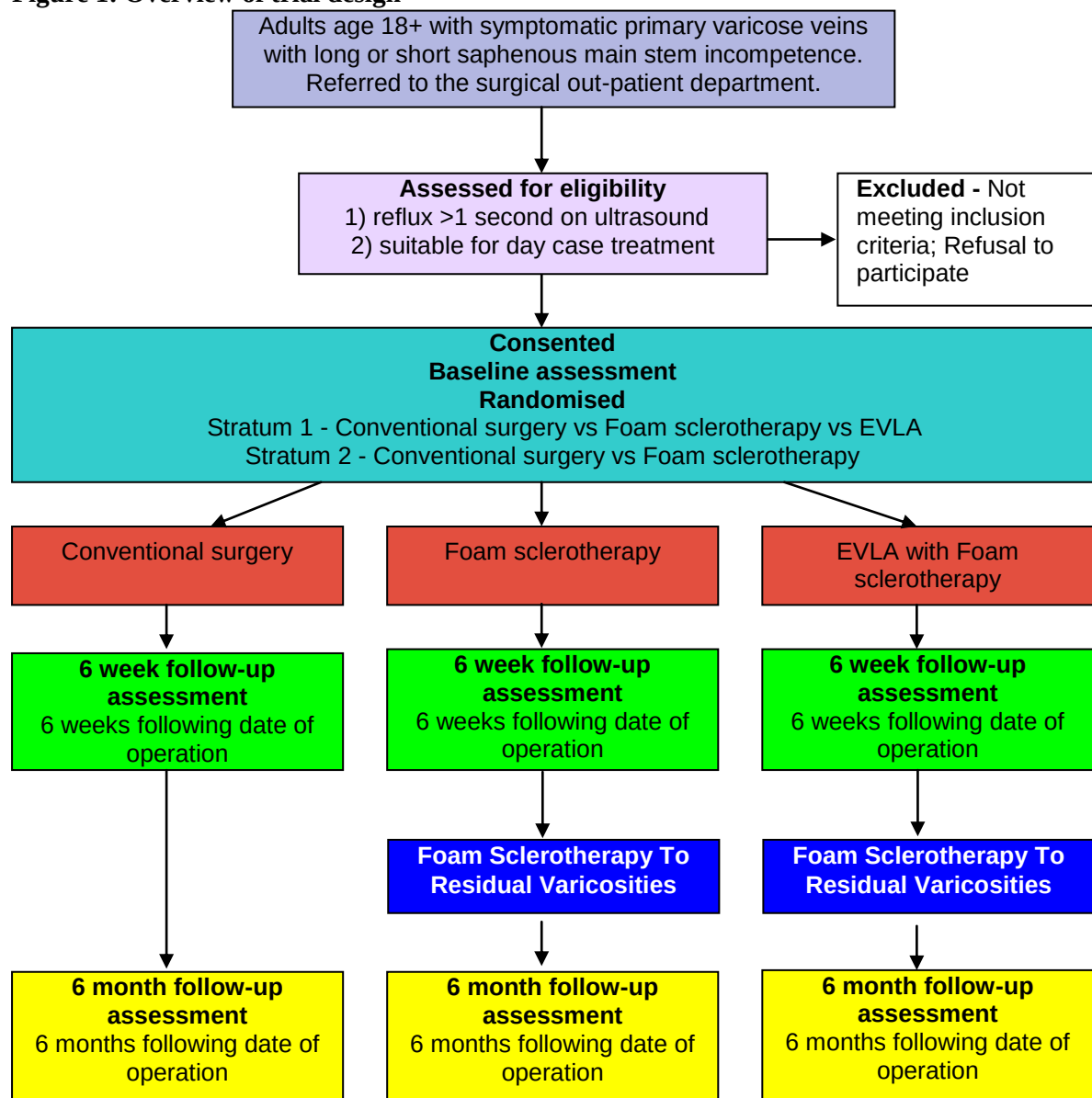
Secondary objectives are to compare the two novel interventions against conventional surgery in respect of:

- Clinical success as determined by residual varicose veins, Venous Clinical Severity Score, complication rates and return to normal activities.
- Technical success (duplex scan verified partial or complete ablation of, or the presence of reflux in, the main long or short saphenous trunk veins) at 6 months (and ultimately through to 5 years). In addition, any development of deep venous incompetence and neovascularisation up to 5 years.
- Cost to the health service and patients of each intervention and any subsequent care.

#### 4. TRIAL DESIGN

This is a multicentre randomised controlled trial of comparing foam sclerotherapy, alone or in combination with endovenous laser therapy, with conventional surgery as a treatment for varicose veins. The trial will initially be conducted in vascular surgery units at 6 hospitals in 5 UK centres (Grampian NHS, Leeds Teaching Hospitals NHS Trust (2 hospitals), Hull Royal Infirmary, the Royal Devon and Exeter Hospital, and Gloucestershire Royal Hospital) and co-ordinated from the Centre for Healthcare Randomised Trials (CHaRT) in the Health Services Research Unit, University of Aberdeen. Additional sites will be added subject to obtaining the necessary approvals. A summary of the trial design is shown in figure 1. The protocol also describes the longer-term follow-up of participants (see section 4.7). The end of clinical follow-up is defined as the completion of six month follow-up for participants. The end of study is defined as the end of funding.

**Figure 1: Overview of trial design**



#### **4.1 Interventions to be evaluated**

Up to three possible treatment options are available:

- 1) conventional surgery;
- 2) foam sclerotherapy of trunk and non-trunk varicosities with further treatment at 6 weeks to residual non-truncal varicosities if required ; and
- 3) endovenous laser ablation of truncal varicosities with foam sclerotherapy of residual non-trunk varicosities at 6 weeks if required.

Patients will enter one of two strata - either (a) one of three treatment options, or (b) one of two treatment options (foam or conventional surgery) depending on which stratum the vascular surgeon has signed up for.

Surgical treatment will be performed as previously described<sup>25</sup>. The aim is to perform sapheno-femoral or sapheno-popliteal ligation, ligate the groin or popliteal tributaries, remove through inversion stripping the incompetent main varicose trunk and to perform phlebectomies for non-truncal varicosities as a combined single procedure.

Foam sclerotherapy involves insertion of a needle into the incompetent long or short saphenous veins under ultrasound control. This is facilitated by placing the patient in the reverse Trendelenberg position<sup>12</sup>. The leg is then raised and sclerosant foam (via 2ml double syringe Tessari technique, 1 part (0.5ml) fibroven and 3 parts (1.5ml) air, with at least 20 passages 3% for main trunk, 1% for non-trunk varicosities) is injected. At each treatment session, the maximum volume of foam that will be administered is 12ml of foam. The aim is to fill the vein with sclerosant with the aid of massage and to avoid entry into femoral or popliteal veins by the use of ultrasound guidance of foam distribution<sup>12</sup>. It is recommended that immediately after injection there is no movement of the patient or leg for 2-5 minutes, no valsalva manoeuvre and no muscle activation. As per the European consensus guidelines a maximum of 12mls of foam will be used at one sitting<sup>16, 26</sup>. Post-procedure compression will be standardised across the study centres. The patient is assessed at 6 weeks to determine the need for further foam sclerotherapy to residual non-trunk varicosities or main stem varicosities. A maximum of 4 treatment sessions of foam sclerotherapy will be offered if required to treat all the varicose veins.

The Fibro-Vein used will be from routine stocks. It will be stored at room temperature or in a refrigerator in a suitably secure location in the ward, clinic or theatre. As is good practice, the storage temperature will be monitored using minimum-maximum thermometers and the minimum and maximum temperatures will be recorded regularly by the study nurse. Any minor temperature deviations will be noted. If the maximum temperature has exceeded 40°C (stability data shows that Fibro-Vein is stable for up to 6 months at 40°C) this will be recorded as a breach, and the Fibro-Vein recalled and destroyed by pharmacy. Careful records will be kept in each centre about which CLASS patients receive Fibro-Vein from which batch.

Endovenous laser ablation involves cannulating the long saphenous vein at the lowest point of incompetence (mid-calf for short saphenous) under ultrasound guidance with the leg to be treated flexed and externally rotated at the hip, and the knee slightly flexed. A guide-wire is first inserted and then a 5Fr catheter passed over this with the tip positioned 0.5-1cm distal to the junction. The laser fibre is inserted as far as the tip of the catheter following which the latter is withdrawn 2cm so that the laser fibre protrudes beyond the catheter. The table is now placed in the Trendelenberg position, and cold saline tumescent with lignocaine is infiltrated along the length of the trunk vein. This provides anaesthesia, compression of vein around catheter, and absorption of heat. The laser fibre is fired continuously during stepwise or continuous withdrawal<sup>27</sup>. The aim is to achieve a target delivery of at least 70 joules per cm. It may be necessary to treat the below knee incompetent long saphenous vein with foam sclerotherapy if laser access is not possible at this site. If required, this will be done at the same treatment session to the level of the mid-calf. Post-procedure compression will be standardised across the study centres. Where appropriate, non-truncal varicosities are treated with foam sclerotherapy at 6 weeks via the use of a butterfly needle

and compression is applied as outlined above. In one of the study sites (Hull) phlebectomies for non-truncal varicosities will be performed at the same time as the laser therapy under local anaesthetic.

## **4.2 Inclusion & Exclusion criteria**

### *Inclusion criteria*

Adult patients (aged over 18 years old) who are referred to the surgical out-patient department for treatment of primary varicose veins with symptomatic (CEAP grade 2 or above) primary long or short saphenous main stem incompetence (reflux >1 second on duplex scanning) are eligible for inclusion.

### *Exclusion criteria*

Current deep vein thrombosis, acute superficial vein thrombosis, allergy to sclerosant, pregnancy or breast feeding, history of hypercoagulability, arterial disease (ankle brachial pressure index <0.8), inability to mobilise post-procedure, needle phobia, long or short saphenous vein less than 3mm in diameter or greater than 15mm<sup>12</sup> and tortuous veins that are considered to be unsuitable for EVLA due to difficulties in passing the guide wire, inability to complete study questionnaires, migraines which are frequent, or migraines which are severe enough to require hospitalisation.

Other exclusion criteria include those specifically mentioned on the fibro-vein (sodium tetradecyl sulphate) prescribing information leaflet which are: varicosities caused by pelvic or abdominal tumours, cardiac failure, pulmonary oedema, local or systemic infection.

All varicose vein treatment should be used with care in patients taking oral contraceptives or hormonal replacement therapy. The treating surgeon will either ask the patient to discontinue the oral contraceptive or hormonal replacement therapy prior to treatment or will prescribe heparin prophylaxis therapy.

Patients who are not fit for a general anaesthetic due to significant systemic disease, morbid obesity or other causes will be excluded from the trial.

## **4.3 Recruitment**

The recruitment process is shown in figure 2. In centres where it is possible, the summary information leaflet will be sent to potentially eligible patients along with the notification of the appointment for their initial consultation. This postal summary information leaflet is based on the summary information leaflet to be handed out at varicose veins clinics that was previously approved by the Ethics Committee. A log will be taken of all patients with primary varicose veins attending the out-patient clinics in order to document the reasons for non-inclusion in the study (venous anatomy, patient co-morbidity, contra-indications to foam sclerotherapy or patients refusal) and to inform the consort diagram. Eligible patients will be identified by the surgeon during their initial consultation, and informed about the different treatments available and the study. As is normal clinical practice, the surgeon will explain the risks and benefits of the treatment options. If the patient is potentially interested in the study, their contact details will be noted and they will be given the study patient information leaflet to take home. If they did not receive the summary information leaflet with their appointment notification, they will be given a copy of this. They will also receive more detailed written information in a leaflet entitled “varicose veins and treatment” which they may they read if they have decided to take part in the study. In some centres, the duplex scan will be undertaken during this initial consultation; in such cases, only those patients who are eligible on the basis of the results of this scan will be informed about the study.

Around one week after the initial consultation, the research nurse will telephone the patient to ascertain whether they are interested in taking part in the study or not. If the patient is interested in taking part in the study, they will be invited to a recruitment appointment at the clinic to

provide informed consent. If the patient did not undergo duplex scanning at the initial appointment, this will be undertaken. They will also be asked to complete a baseline questionnaire. In some circumstances (for example where the duplex scan was completed at the initial consultation and the patient lives a considerable distance from the recruitment clinic and would find it problematic to travel to a recruitment appointment), the research nurse can suggest to the patient that recruitment and baseline assessment could be done by post. In such circumstances, the consent form would be sent to the patient to complete at home, together with the baseline questionnaire. The research nurse would be available by telephone, to answer any questions or explain details about the study.

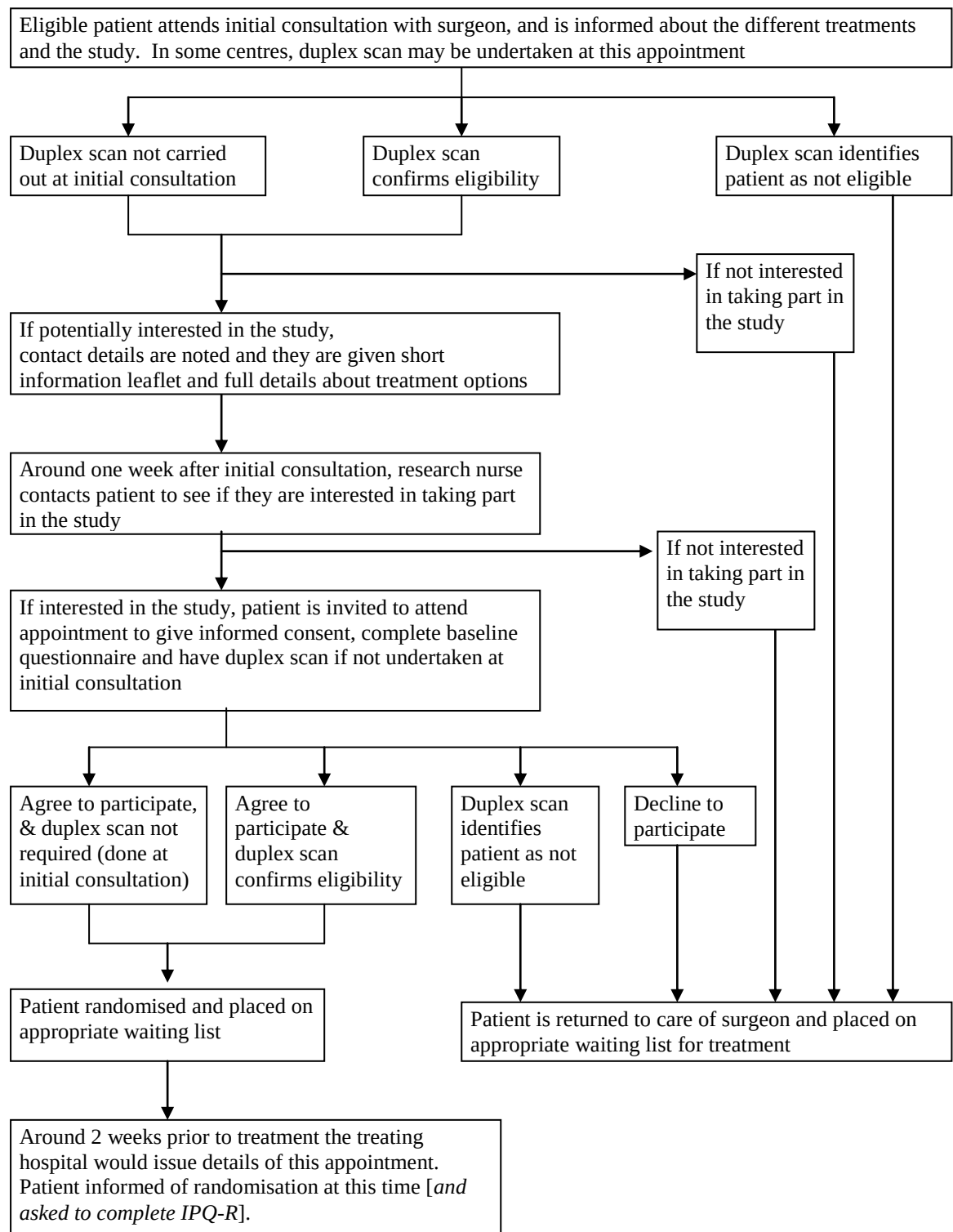
In the presence of bilateral disease, the more severely affected leg, as determined by the participant, will be nominated as the study leg, and the other leg will, where possible, have the same intervention as the study leg. Randomisation will be stratified by unilaterality/bilaterality.

#### **4.4 Randomisation**

Eligible participants who have consented to participate will be randomised using the proven telephone Interactive Voice Response (IVR) randomisation application hosted in the study data centre at the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen. CHaRT will also host a linked web-based randomisation service. Each of these two strata (based on treatment options available at the trial centre - surgery, foam and laser, or surgery and foam) will have its own separate randomisation application,. A minimisation algorithm using centre, age ( $<50$ ,  $\geq 50$ ), gender, short or long saphenous vein, and unilateral or bilateral (common for both strata) will be used. It is expected that all participants within a particular hospital will only ever take part in one of the strata.

Once randomised, patients will be placed on the appropriate waiting list. However, the patient will not be informed of their randomisation at this stage. Around two weeks prior to treatment, an appointment for treatment will be issued by the hospital - at this time the patient will be informed of their randomisation. The delay in informing participants about their randomisation is in an attempt to minimise the possibility of unequal drop-out between the arms.

On trial entry, the participant's GP will be informed that they have agreed to participate. At the same time that the participant is informed of their randomisation, the GP will also be informed.

**Figure 2: Identification and recruitment of eligible patients**

#### 4.5 Delivery of interventions

These will be delivered as described above in 4.1.

Six weeks after treatment, participants will be reviewed at an outpatient clinic. Participants who underwent foam sclerotherapy will be assessed to determine the need for further foam sclerotherapy to residual non-trunk varicosities or main stem varicosities. Participants who underwent EVLA will, where appropriate, have non-truncal varicosities treated with foam sclerotherapy via the use of a butterfly needle and compression is applied as outlined above.

#### 4.6 Proposed outcome measures

##### Primary outcome measures

We will assess outcomes up to 6 months, but with possible long-term follow-up to 5 years through a separate funding application.

1. Primary patient outcome: Disease specific (Aberdeen Varicose Vein Questionnaire) and generic quality of life (EQ-5D, SF-36) at 6 months and 5 years
2. Primary economic outcome: Incremental cost per quality adjusted life years (QALY) at 6 months and 5 years

##### Secondary outcome measures

1. Costs to the health service and patients and any subsequent care.
2. Technical success of venous intervention at 6 weeks, 6 months and 5 years
3. Clinical success of venous intervention at 6 weeks, 6 months and 5 years
4. Disease specific and generic quality of life at 6 weeks
5. Behavioural recovery (see section 5.3 for details)

#### 4.7 Measurement of outcomes

The timing and instruments to be used for data collection is summarised in table 1.

1. Quality of life assessment: Disease specific (Aberdeen Varicose Vein Questionnaire) and generic quality of life (EQ-5D+SF-36) will be collected by patient self-completed questionnaires at the following time points: baseline, 6 weeks, 6 months and yearly up to 5 years post-initial treatment.
2. Technical success: Duplex scanning will be performed by an independent fully trained technician at 6 weeks, 6 months and 5 years. Centralised training for each of these study technicians will be provided and the procedure standardised so that specific anatomical segments are examined for patency/obliteration, and reflux (defined as being greater than one second). Whenever possible, an individual patient will be scanned by the same technician using the designated study scanner. An independent ultrasonographer will assess the first ten video-recorded scans performed by each individual technician participating in the study and thereafter at least one scan per month per centre.
3. Clinical success: Venous Clinical Severity Score. Presence of residual varicosities as scored by the patient and an independent assessor on a visual analogue score (VAS) will be conducted at 6 weeks, 6 months and 5 years.
4. Length of time to return to normal activity and work, and patient satisfaction with treatment will be collected within the patient self completed questionnaires at 6 weeks.
5. Complication rates: wound infection, haematoma, nerve injury, skin staining, thrombophlebitis, deep venous thrombosis will be assessed at 6 weeks and 6 months
6. Incremental cost per QALY: at six months, 5 years and over the patient's lifetime.
7. Behavioural recovery: assessed by self completed behavioural recovery questionnaire at 6 weeks (see section 5.3).

The majority of questionnaires completed by participants will be completed during a clinic visit. If there is insufficient time to allow completion at the clinic, questionnaires will be given to the participant to take home. If they are not returned, a reminder will be sent in three weeks. If the questionnaire is not returned after a further two weeks, a telephone reminder will be made. If a

participant fails to attend a clinic visit, they will be sent the appropriate questionnaire to complete. If there is no response, a reminder will be sent three weeks after the questionnaire was sent and a telephone reminder made after a further two weeks.

**Table 1 - timing of instruments**

| <b>Time-point</b>                     | <b>CRFs - completed by participant</b>                                                                                                                                                                                                                                                                                 | <b>CRFs / procedures - completed by research nurse/clinician/technician</b>                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial consultation                  |                                                                                                                                                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>• Duplex scan (in some centres)</li> <li>• Short/long saphenous vein; uni- or bi-lateral; venous clinical severity score (VCSS)</li> <li>• CEAP classification</li> </ul> <p><b>NB</b> - this data is collected as routine at a patients initial consultation; if they agree to participate in the study, data will be collated onto CRFs by research nurse.</p> |
| Recruitment                           | Questionnaire completed at <b>clinic</b> including: <ul style="list-style-type: none"> <li>• Aberdeen Varicose Veins Questionnaire</li> <li>• EQ-5D</li> <li>• SF-36</li> <li>• Questions based on common-sense self-regulation model</li> </ul>                                                                       | <ul style="list-style-type: none"> <li>• Personal details, GP, best contact etc</li> <li>• Duplex scan (if not done at initial consultation)</li> <li>• Baseline demographic factors</li> </ul>                                                                                                                                                                                                         |
| After randomisation, before treatment | Questionnaire completed by <b>post</b> including: <ul style="list-style-type: none"> <li>• Questions based on common-sense self-regulation model</li> </ul>                                                                                                                                                            | None - participant not at clinic                                                                                                                                                                                                                                                                                                                                                                        |
| At treatment appointment(s)           | Visual analogue scale completed at clinic assessing pain of procedure                                                                                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>• Procedural details</li> <li>• Complications of procedure</li> </ul>                                                                                                                                                                                                                                                                                            |
| 6 weeks after treatment               | Questionnaire completed at <b>clinic</b> including: <ul style="list-style-type: none"> <li>• Aberdeen Varicose Veins Questionnaire</li> <li>• EQ-5D</li> <li>• SF-36</li> <li>• Time to return to work/normal activity</li> <li>• Satisfaction with treatment</li> <li>• Behavioural recovery questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>• Presence/absence deep-vein thrombosis</li> <li>• Presence/absence residual varicosity</li> <li>• Technical success (duplex scanning)</li> <li>• VCSS</li> <li>• Complications</li> <li>• For patients treated with EVLA or foam, details of further foam injections</li> </ul>                                                                                 |
| 6 months after treatment              | Questionnaire completed at <b>clinic</b> including: <ul style="list-style-type: none"> <li>• Aberdeen Varicose Veins Questionnaire</li> <li>• EQ-5D</li> <li>• SF-36</li> <li>• Questions based on common-sense self-regulation model</li> <li>• Economic questions</li> </ul>                                         | <ul style="list-style-type: none"> <li>• Presence/absence deep-vein thrombosis</li> <li>• Presence/absence residual varicosity</li> <li>• Technical success (duplex scanning)</li> <li>• Complications</li> <li>• VCSS</li> </ul>                                                                                                                                                                       |

| <i>Time-point</i>                    | <i>CRFs - completed by participant</i>                                                                                                                                                                                                                                                                                | <i>CRFs / procedures - completed by research nurse/clinician/technician</i>                                                                                                                                                                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yearly up to 4 years after treatment | Questionnaire completed at <b>home</b> <ul style="list-style-type: none"> <li>• Aberdeen Varicose Veins Questionnaire</li> <li>• EQ-5D</li> <li>• SF-36</li> <li>• Questions based on common-sense self-regulation model</li> <li>• Satisfaction with treatment</li> <li>• Economic questions</li> </ul>              |                                                                                                                                                                                                                                                                                             |
| 5 year follow-up                     | Questionnaire completed at <b>clinic</b> including: <ul style="list-style-type: none"> <li>• Aberdeen Varicose Veins Questionnaire</li> <li>• EQ-5D</li> <li>• SF-36</li> <li>• Questions based on common-sense self-regulation model</li> <li>• Satisfaction with treatment</li> <li>• Economic questions</li> </ul> | <ul style="list-style-type: none"> <li>• Presence/absence deep-vein thrombosis</li> <li>• Presence/absence residual varicosity</li> <li>• Technical success (duplex scanning)</li> <li>• VCSS</li> <li>• Complications</li> <li>• details of further treatment of varicose veins</li> </ul> |

#### 4.8. Safety

We aim to report serious adverse events in accordance with the guidance from the EC on this issue (see

<http://eudract.emea.eu.int/docs/Detailed%20guidance%20collection%20of%20adverse%20events.pdf>)

##### 4.8.1 Serious adverse event (definition)

A serious adverse event is defined as any medical occurrence that:

- Results in death
- Is life threatening (ie the subject was at risk of death at the time of the event)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition

These adverse events include any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

##### 4.8.2 Adverse reaction (definition)

An adverse reaction is an adverse event judged either by the reporting investigator or the sponsor as having a reasonable **causal** relationship to the medicinal product.

##### 4.8.3 Unexpected adverse reaction (definition)

An adverse reaction, the nature and severity of which is not consistent with the applicable production information. In this study, the following serious adverse events are potentially “expected”.

- Deep vein thrombosis [following foam sclerotherapy, laser treatment, surgery]
- Pulmonary embolism [following foam sclerotherapy, laser treatment, surgery]
- Anaphylactic shock [following foam sclerotherapy]
- Stroke [following foam sclerotherapy]
- Retinal arteriole occlusion [following foam sclerotherapy]

- Myocardial infarction [following foam sclerotherapy]
- Cutaneous necrosis and ulceration [following foam sclerotherapy]
- Epileptic fit [following foam sclerotherapy]
- Intra-arterial injection [following foam sclerotherapy]
- Injury to a major artery (common femoral or superficial femoral artery) [following surgery]
- Injury to a major vein (common femoral or popliteal vein) [following foam sclerotherapy, laser treatment or surgery]
- Injury to a motor nerve (femoral, tibial or peroneal nerve) [following surgery]
- Transient Ischemic Attack [following foam sclerotherapy]
- Migraine (following foam sclerotherapy)

All other serious adverse events are unexpected.

#### **4.8.4 Procedure for adverse event reporting in this study.**

The patient will be advised to contact their General Practitioner should they experience an adverse event between the period following treatment and the six week follow-up study appointment. This is current clinical practice for patients receiving surgery, laser therapy or foam sclerotherapy within the NHS.

##### **a. Non serious adverse events**

At each visit, the research nurse or investigator should ask if there have been any adverse medical events since the last visit. All adverse medical events reported by the patient should be noted in the patient's hospital notes, together with a note of the date of starting, the duration, and any medical treatment received. There is no need to report these adverse (non-serious) events as part of the study data collection.

##### **b. Serious adverse events**

All serious adverse events should be reported.

- i. If the adverse event is **serious but potentially expected** (see 4.8.3 above for list of potentially expected serious adverse events), a **serious adverse event report form** should be completed within **seven days**. If the web-based form is completed, the Chief Investigator will be notified automatically. If a paper based form is used, one copy should be faxed to the Chief Investigator, Dr Julie Brittenden, at 01224 552553, and to CHaRT on 01224 554580.
- ii. If the adverse event is **serious and unexpected** (see 4.8.3 above for list of potentially expected serious adverse events), a **serious adverse event report form** should be completed **within 24 hours** of the local investigator being aware of the event. If the web-based form is completed, the Chief Investigator will be notified automatically. If a paper based form is used, one copy should be faxed to the Chief Investigator, Dr Julie Brittenden, at 01224 552553, and to CHaRT on 01224 554580.

#### **4.8.5 Serious adverse event or serious adverse reaction?**

A serious adverse event is a serious adverse reaction if the event has a reasonable **causal** relationship to the medicinal product. The local PI should, as soon as possible after a serious adverse event is identified, use his or her judgement to determine whether the event is likely to have been caused by study treatment.

After a serious adverse event, the PI should, therefore, using the web-based form, complete the section on likely causality. If the PI believes that the serious adverse event is a serious adverse **reaction** (ie that the study drug was reasonably likely to have caused the adverse event), he/she will complete the CIOMS form and fax or e-mail to the Chief Investigator, Dr Julie Brittenden, at (fax) or [j.brittenden@abdn.ac.uk](mailto:j.brittenden@abdn.ac.uk).

#### 4.8.6 Reporting responsibilities of the Chief Investigator

**i. *Fatal or life threatening SUSARs***

Julie Brittenden as Chief Investigator will forward reports on fatal or life threatening suspected unexpected serious adverse reaction (SUSARs) (ie serious unexpected adverse events where a causal link between the drug and the event is suspected) to the MHRA and the Research Ethics Committee (Scotland A) within **seven** days of first knowledge of the minimum criteria (ie within seven days of the event becoming apparent) using the relevant proforma. A copy will be sent to the sponsor (University of Aberdeen) and to [*the manufacturer*]. Follow up information will be forwarded to the MHRA and ethics committee within eight days.

**ii. *Non fatal and non life-threatening SUSARs***

Julie Brittenden will forward reports on non fatal and non life-threatening SUSARs to the MHRA and the Research Ethics Committee (Scotland A) within fifteen days of first knowledge of the minimum criteria (ie within **fifteen** days of the event becoming apparent) using the relevant proforma. A copy will be sent to the sponsor (University of Aberdeen), and to [*the manufacturer*]. Follow up information will be forwarded to the MHRA and ethics committee within eight days.

**iii. *All other serious adverse events***

ChART with the help of the CI will prepare a summary of all serious adverse events every 4 months for participating investigators and distribute and discuss at steering group meetings. Copies will be sent to [*the manufacturer*] and to the DMC. On an annual basis, serious adverse event reports will be sent to the MREC, the MHRA and the sponsor.

#### 4.9 Data management

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Patient's details will be stored on a database under the guidelines of the 1988 Data Protection Act. Patients will be allocated an individual specific study number and their details will be stored on the study database.

Clinical data will be entered into the database by the research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to ChART will be entered there.

Staff in the study office will work closely with local Research Nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

#### 5. Analysis

##### 5.1 Statistical analysis

Two comparisons will be considered for the main trial analysis – (1) surgery group versus foam sclerotherapy group and (2) surgery group versus EVLA. For the main trial analyses, the primary and secondary outcomes will be compared using generalised linear models, with adjustment for minimisation variables (age <50; gender; short or long saphenous vein; unilateral or bilateral) and participant baseline values where appropriate. Statistical significance will be at the 5% level and corresponding confidence intervals will be derived. All participants will remain in their allocated group for analysis (intention to treat). Subgroup analyses (through the use of tests for interaction) will explore the possible effect modification of a number of factors (age <50; gender; short or long saphenous vein; unilateral or bilateral; and venous severity score (<15)<sup>33</sup>), all using stricter levels of statistical significance ( $p < 0.01$ ). For the process evaluation, process variables that are correlated with the primary outcome (at 5% significance) will be included as covariates in a model that includes treatment effect to test whether the process variables (such as scores on self

regulation and behaviour recovery questionnaires) can explain a significant proportion of the treatment effect. All study analyses will be according to a statistical analysis plan that will be agreed in advance by the Trial Steering Committee. A single main analysis will be performed at the end of the trial when all follow up has been completed. An independent Data Monitoring Committee (DMC) will meet early in the trial to agree its terms of reference and other procedures and will review confidential interim analyses of accumulating data at least annually.

## **5.2 Economic evaluation**

A formal economic evaluation will be undertaken to assess the relative cost-effectiveness (assessed in terms of incremental cost per QALY) of the treatments. This will take the form of a Markov model which will describe pathways of care that patients may follow from the initial surgical interventions. The data from the trial will be the main source of data but further data with which to model outcomes beyond a 6 month follow-up will be systematically derived from the literature and other existing data sources. The assembly of these further data will follow guidelines for best practice. The perspective of the model and within trial analyses will be the patient and the NHS. The results of the analyses will be presented as point estimates of mean incremental costs, effects, and, incremental cost per QALY. Sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. This will be accomplished using probabilistic and deterministic sensitivity analyses to address parameter and other forms of uncertainty. Similarly, for the within trial analysis, techniques such as bootstrapping will be used alongside deterministic sensitivity analyses to address uncertainty. In both the model and within trial analyses the cost per QALY data will be presented in terms of cost-effectiveness acceptability curves (CEACs).

### ***Collection of data***

Data collection from the trial will focus on estimating the use of secondary care, primary care and personal costs to individuals (such as time and travel costs). In addition, health state valuations will be obtained from the EQ-5D and SF-6D (derived from the responses to the SF-36).

At 6 months after randomisation patients will provide information about their use of primary care health services (via the health care utilisation questions). At the end the trial follow-up patient's notes will be reviewed and the case note review form completed in order to determine the use of secondary care health services.

At baseline, 6 weeks and 6 months, they will complete the EQ 5D and SF-36.

### ***Participant costs of varicose veins treatment***

Participant costs will comprise three main elements: self purchased healthcare; travel costs for making return visit(s) to NHS health care; and time costs of traveling and attending NHS care.

- Self-purchased health care is likely to include items such as prescription costs and over the counter medications. Information on these costs will be collected via the health care utilisation questionnaire (at 6 months)
- Estimation of travel costs requires information from participants about the number of visits to, for example, their GP (estimated from the health care utilisation questionnaire) and the unit cost of making a return journey to each type of health care provider (from Patient Costs Questionnaire at 6 months)
- The cost of participant time will be estimated in a similar manner. The participant will be asked, in the Patient Costs Questionnaire, how long they spent traveling to and attending their last visit to each type of health care provider. Participants will also be asked what activity they would have otherwise been undertaking (e.g. paid work, housework, leisure activities) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours, and costed using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time. These unit time costs, measured in terms of their natural and monetary terms will then be combined with

estimates of the number of health care contacts derived from the Health Care Utilisation Questionnaire.

#### ***Health service resource use***

The use and cost of health services can be divided into 3 components:

- the cost of intervention
- the use of secondary care services after the intervention until the end of follow-up
- the use of primary care services (including medications) following surgery

#### ***Costs of intervention***

Health service costs incurred as the consequence of the intervention will be recorded. Main areas of costs will be staffing (operating theatre staff costs), capital costs (buildings and equipment) and consumables. Also included in this cost will be the use of other services during the period spent in hospital following the procedure. These will include:

- Consumables (drugs, etc)
- Staff time (GP, practice nurse etc)
- Outpatient visits
- Hospital admissions

Unit costs for these resources will be based on nationally available data and study-specific estimates. Longer term estimates of resource use and cost will be derived from trial estimates and, as noted above, the literature.

#### ***Other Secondary care costs***

As described above secondary care resource use will be elicited by case note review; The data collected will be:

- Other operations in time period
- Visits to other specialties in time period, for example, physiotherapy etc.

Unit costs for these resources will be based on nationally available data and study-specific estimates. Longer term estimates of resource use and cost will be derived from trial estimates and, as noted above, the literature.

#### ***Primary care costs***

Primary care resource use will be obtained from patient completed questionnaires completed at 6 months. Data collected will be:

- Number of GP/nurse consultations in past 6 months
- Information of prescriptions
- Information on any private health care use in last 6 months

As described above unit costs for these resources will be based on nationally available data and study-specific estimates.

#### ***Cost effectiveness***

Two analyses will be presented: (a) a within trial analysis and (b) an economic model. The economic model will be the primary analysis as it will extrapolate the results of the trial to a longer follow-up period.

#### ***Within trial analysis***

Primary measures of effectiveness in the within trial analysis will be quality adjusted life years (QALYs) which will be estimated from the responses to the EQ-5D, valued using the UK population tariffs. To test the robustness of the outcome measure and to enable comparison with the only other published UK based economic evaluation in this area, QALYs will also be

estimated using responses from the SF36 (converted into the SF-6D). For each intervention, the area under the curve will be calculated to measure the QALY gain for each patient.

For the within trial analysis total NHS and total patient costs will be estimated for each participant. Incremental cost per QALY estimates will be estimated using the costs and QALY data. Methods such as bootstrapping will be used to produce credible intervals around estimates of mean incremental costs, QALYs and cost-effectiveness.

#### *Model based analysis*

While the within study results will prove useful, it is important to note that the effects of treatment on costs and outcomes may persist into the future. Additional information will be gained through modeling the costs and outcomes which consider a longer time horizon. The model will be based on care pathways, identifying key measures of clinical outcome and resource use. The care pathways will be developed in consultation with clinical members of the team and the literature. These pathways along with lessons learnt from previous economic evaluations will be developed in the economic model. The model structure will describe the logical and temporal sequence of events from the initial surgery until the patient's death. Thus in the model, the findings of the trial will be extrapolated to the patient's lifetime. Additional data required for the economic model will be systematically assembled using recognised methods for their assembly (Phillip Z et al HTA monograph). The assembly of this data will involve either systematic reviews or, some parameters such as cost and outcomes data, focused searches of sources relevant to the UK.

The results of the analyses will be presented as point estimates of mean incremental costs, QALYs, and, incremental cost per QALY. Sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. This will be accomplished using probabilistic and deterministic sensitivity analyses to address parameter and other forms of uncertainty. Cost per unit of health effect and cost per QALY data will be presented in terms of cost-effectiveness acceptability curves (CEACs).

### **5.3 Process evaluation**

As it will not be possible for participants to be blinded to their treatment, several steps will be taken to increase our confidence in the trial results based on the primary quality of life outcomes. As much as possible, information provided to participants at recruitment, after randomisation and following treatment will be standardised. Nevertheless, we expect variation between participants in terms of their cognitive and emotional representations of:- their condition; the different treatments; and the associated risks.

These forms of variation will result in participants having different preferences (e.g. for general anaesthetic or not; for a one-off treatment versus the possibility of repeated treatment sessions; for less invasive procedures). Whether participants are then randomised to receive their preferred treatment or not will have consequences for their emotional reactions and expectations about their recovery trajectory. These emotional and cognitive processes may influence recovery directly<sup>29</sup> or may influence behaviours that impact on recovery<sup>30</sup>. The emotional and cognitive factors are represented in the Common Sense Self Regulation Model in response to a health threat (CSSRM)<sup>31</sup>. Questionnaires based on this model will be administered twice at baseline (at recruitment and then after randomisation but before treatment) and at 6 months after randomisation.

The key behavioural milestones during recovery after treatment for varicose veins (eg first occasion of walking; driving; returning to work) will be identified from a small number of focus group interviews with patients who have received treatment for varicose veins approximately 6 weeks previously. Data from these interviews will be used to develop a behavioural recovery questionnaire, which will be administered to trial participants at the 6-week follow up. This will identify the pace of recovery at the level of specific behaviours.

The theoretical basis of the outcome assessments is also important. The WHO International Classification of Functioning, Disability and Health (ICF) (WHO, 2002), distinguishes Impairment (I) (structural or functional), Activity Limitations (A) and Participation Restrictions (P). Using the technique of Discriminant Content Validity (DCV), we will identify those items in the Aberdeen Varicose Veins Questionnaire and the “Patient Symptoms and Concerns Questionnaire” that are ‘pure’ measures of I, A and P. We expect that these three dimensions will not be perfectly correlated with each other and that both the surgical interventions and the psychological process variables will differentially predict them.

## 6. Sample size

### 6.1 Proposed sample size

Patients will be randomised to either stratum (a) one of three treatment options, or stratum (b) one of two treatment options (foam or conventional surgery) depending on which stratum the vascular surgeon has signed up for. Four hospitals are prepared to contribute to stratum (a) and 2 hospitals to stratum (b) (table 2). It is expected that all participants within a particular hospital will only ever take part in one of the strata. The proposed sample sizes are shown in the table below giving a total of 1015 participants (justification of sample size given below).

**Table 2: target recruitment in each of the strata**

|                           | <b>Conventional surgery</b> | <b>Foam</b> | <b>EVLA</b> |
|---------------------------|-----------------------------|-------------|-------------|
| Stratum (a) (4 hospitals) | 245                         | 245         | 245         |
| Stratum (b) (2 hospitals) | 140                         | 140         | -           |
| Total                     | 385                         | 385         | 245         |

Based on previous studies<sup>10, 32</sup>, it would be reasonable to expect differences between surgery and minimally invasive treatment (foam or EVLA) of approximately 0.25 of a standard deviation on the quality of life instruments at 6 months follow up (in particular, this would equate to a 5 point shift in the EQ-5D score). This estimated difference in standard deviation was observed in SF-6D and EQ-5D scores in the small trial<sup>10</sup> by Ratcliffe that compared conventional surgery with sclerotherapy.

Conventional surgery versus foam: For this primary comparison stratum (a) and (b) can be combined without introducing any bias. A trial with 385 patients in each group (total 770) will have at least 90% power at a 5% significance level to detect a difference of 0.25 standard deviations change in both Aberdeen Varicose Vein Score and EQ-5D. Adjusting for baseline score allows the sample size to be decreased by a factor of 1- correlation squared, so 385 participants allows for a 10% loss to follow up at 6 months (assuming a correlation between baseline and 6 month scores of at least 0.31). A correlation of 0.31 is in our experience conservative for quality of life studies, but should the loss to follow up be 15%, the study would still have 90% power to detect a difference of 0.25 standard deviations. Cost savings will be sensitive to the number of participants with recurrent varicose veins requiring re-intervention in each group. Allowing for additional loss to follow-up (up to 20%) by 5 years, the study will have 90% power to detect a 15% difference in recurrence from 32% in conventional surgery to 45% in the other groups (which would be funded separately).

Conventional surgery versus EVLA: For this primary comparison only participants in stratum (a) provide a direct randomised comparison giving 245 participants in each group (490 in total). This trial will have 80% power at 5% significance to detect a difference of 0.25 standard deviations. Given adjustment for baseline measures this allows for a 10% loss to follow up.

### 6.2 Expected loss to follow up

Loss to follow up in previous trials was approximately 12% at 12 months<sup>10, 32</sup>. We anticipate fewer losses to follow up for several reasons. Follow up is only at 6 months, is clinic based, therefore, less reliant on postal questionnaires. Methods to minimise this include automated reminders system, self completion of questionnaires at clinics combined with postal questionnaires and collating 'best contacts' information.

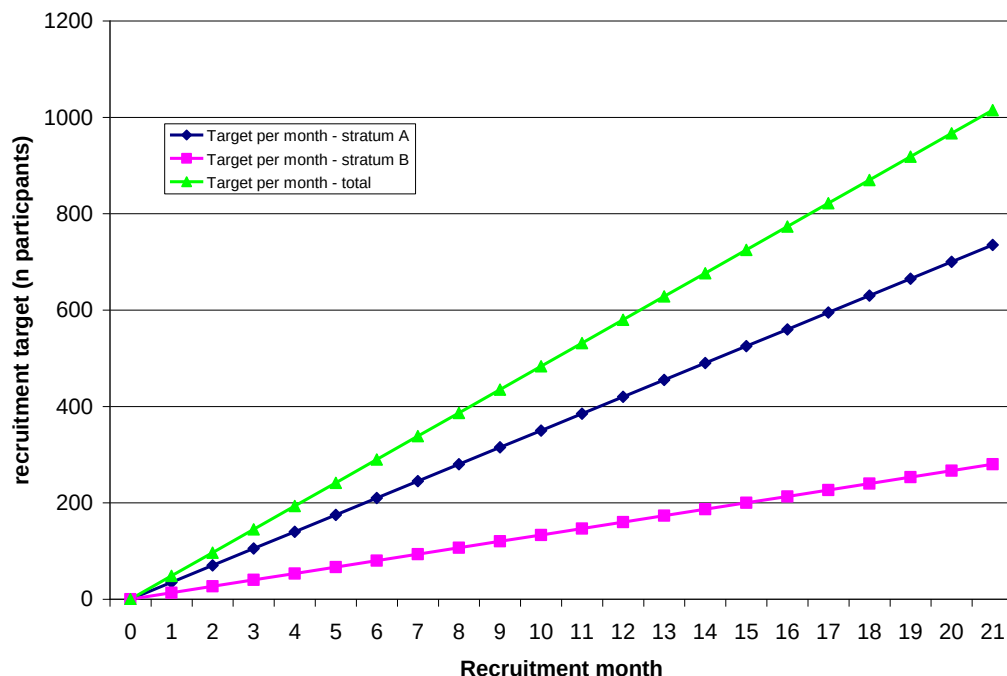
### 6.3 Recruitment rates and expected throughput per centre

Data and correspondence from the participating centres, cross-validated using 2005/6 Hospital Episode Statistic data, indicate approximately 70% of referrals for varicose vein surgery will be eligible for treatment of primary varicose veins. This was further confirmed from a pilot study in Aberdeen that identified that 365/515 (71%) of patients presenting to the venous clinic with primary varicose veins were suitable for EVLA. Conservatively, we expect 50% of these eligible patients will be willing to be randomised (a 50% rate was found in the Ratcliffestudy<sup>10</sup>).

For stratum (a), we require 735 participants. The combined throughput of the 4 centres involved in stratum (a) is 1350 per annum (confirmed by Hospital Episode Statistic data). Using these assumptions, we should be able to recruit 827 participants over 21 month recruitment period. However, allowing for a further 10% being missed due to staff illness or annual leave we anticipate recruiting 735 participants in 21 months. For stratum (b), we require 280 participants from the additional 2 centres. The combined throughput for these centres is 600 per annum. Using our assumptions, we should be able to recruit 367 participants in 21 months. Again, assuming some will be missed, we will be able to recruit 280 over 21 months.

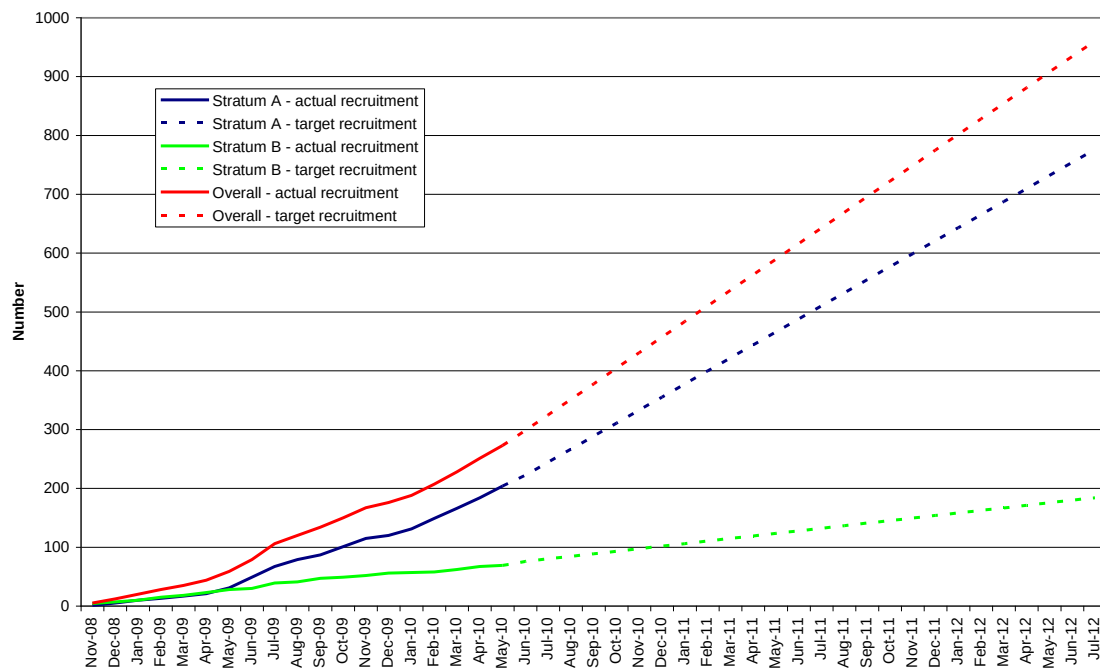
Target recruitment rates are shown in figure 3.

**Figure 3: Recruitment targets**



### 6.4 Revised recruitment rates

The HTA approved an extension to the recruitment period of 24 months to meet recruitment targets. The revised recruitment targets are shown in Figure 4.

**Figure 4: Revised recruitment targets**

A log of all patients with primary varicose veins who attend the clinic will be completed. This will allow data to be obtained regarding the number of patients who are eligible for all three treatments and reasons for exclusion (venous anatomy, patient co-morbidity, contra-indications to foam sclerotherapy or patients refusal).

## 7. Ethics and governance

### 7.1 Ethical arrangements

Ethics committee approval and written informed consent will be obtained. The study patient information sheet will provide details of the anticipated risks and benefits of taking part in the study. In addition all patients will receive leaflets detailing the proposed treatment modalities as is our current practice. Patients will be reassured that all data which are collected during the course of the research will be kept strictly confidential. Patient's details will stored on a database under the guidelines of the 1988 Data Protection Act. We will also seek the patient's permission to inform their general practitioner that they are taking part in this study.

### 7.2 MHRA Approval

MHRA approval is required, and as recommended by the National Institute for Health and Clinical Excellence<sup>34</sup> special arrangements for consent for the use of foam sclerotherapy have been obtained from the clinical governance leads within the each of the collaborating NHS Trusts. An independent data monitoring committee will monitor emerging data from the study.

### 7.3 Research Governance

As per HTA requirements a Trial Steering Group (TSC) and an independent Data Monitoring Committee (DMC) will be set up. Membership of these committees has already been considered and no overseas members are expected. It is anticipated that both the TSC and the DMC would meet at least annually.

### 7.4 Sponsorship

The University of Aberdeen will act as the sponsor for the trial.

**8. Project timetable and milestones**

Study duration - 36 months

Milestones: Months 1-6: initiation of study, recruitment of staff;

Months 6-27: patient recruitment;

Months 27-33: completion of 6 month patient follow up;

Months 33-36: analysis of data, economic analysis, interpretation of results and writing report

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