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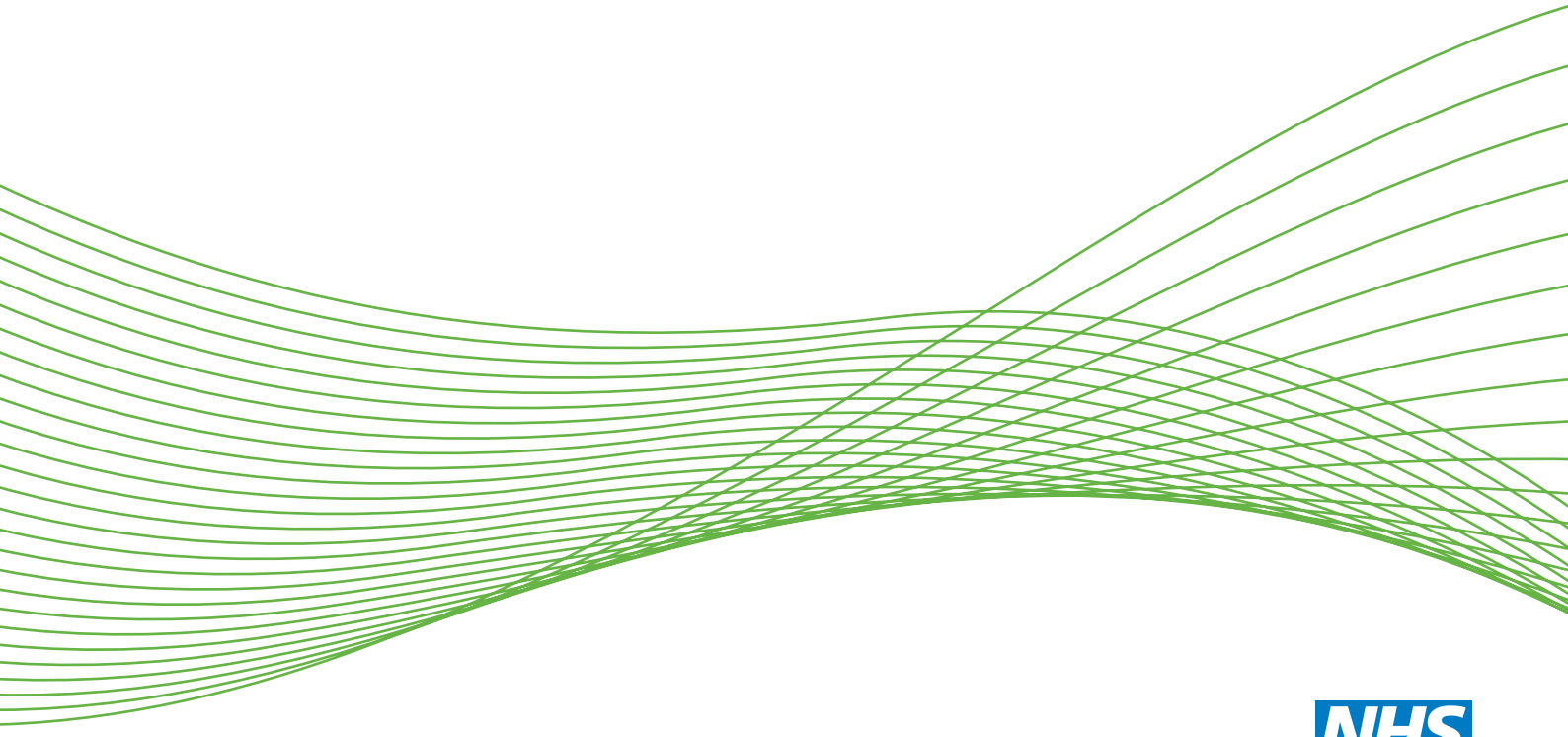

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Abstract

Clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation and surgery for varicose veins: results from the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) randomised controlled trial

Julie Brittenden,[1*] Seonaidh C Cotton,[2] Andrew Elders,[2] Emma Tassie,[3] Graham Scotland,[2,3] Craig R Ramsay,[2] John Norrie,[2] Jennifer Burr,[4] Jill Francis,[5] Samantha Wileman,[2] Bruce Campbell,[6] Paul Bachoo,[1] Ian Chetter,[7] Michael Gough,[8] Jonothan Earnshaw,[9] Tim Lees,[10] Julian Scott,[8] Sara A Baker,[11] Graeme MacLennan,[2] Maria Prior,[2] Denise Bolsover[2] and Marion K Campbell[2]

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Background: Foam sclerotherapy (foam) and endovenous laser ablation (EVLA) have emerged as alternative treatments to surgery for patients with varicose veins, but uncertainty exists regarding their effectiveness in the medium to longer term.

Objectives: To assess the clinical effectiveness and cost-effectiveness of foam, EVLA and surgery for the treatment of varicose veins.

Design: A parallel-group randomised controlled trial (RCT) without blinding, and economic modelling evaluation.

Setting: Eleven UK specialist vascular centres.

Participants: Seven hundred and ninety-eight patients with primary varicose veins (foam, $n = 292$; surgery, $n = 294$; EVLA, $n = 212$).

Interventions: Patients were randomised between all three treatment options (eight centres) or between foam and surgery (three centres).

Primary outcome measures: Disease-specific [Aberdeen Varicose Vein Questionnaire (AVVQ)] and generic [European Quality of Life-5 Dimensions (EQ-5D), Short Form questionnaire-36 items (SF-36) physical and mental component scores] quality of life (QoL) at 6 months. Cost-effectiveness as cost per quality-adjusted life-year (QALY) gained.

Secondary outcome measures: Quality of life at 6 weeks; residual varicose veins; Venous Clinical Severity Score (VCSS); complication rates; return to normal activity; truncal vein ablation rates; and costs.

Results: The results appear generalisable in that participants' baseline characteristics (apart from a lower-than-expected proportion of females) and post-treatment improvement in outcomes were comparable with those in other RCTs. The health gain achieved in the AVVQ with foam was significantly lower than with surgery at 6 months [effect size −1.74, 95% confidence interval (CI) −2.97 to −0.50; $p = 0.006$], but was similar to that achieved with EVLA. The health gain in SF-36 mental component score for foam was worse than that for EVLA (effect size 1.54, 95% CI 0.01 to 3.06; $p = 0.048$) but similar to that for surgery. There were no differences in EQ-5D or SF-36 component scores in the surgery versus foam or surgery versus EVLA comparisons at 6 months.

The trial-based cost-effectiveness analysis showed that, at 6 months, foam had the highest probability of being considered cost-effective at a ceiling willingness-to-pay ratio of £20,000 per QALY. EVLA was found to cost £26,107 per QALY gained versus foam, and was less costly and generated slightly more QALYs than surgery. Markov modelling using trial costs and the limited recurrence data available suggested that, at 5 years, EVLA had the highest probability ($\approx 79\%$) of being cost-effective at conventional thresholds, followed by foam ($\approx 17\%$) and surgery ($\approx 5\%$).

With regard to secondary outcomes, health gains at 6 weeks ($p < 0.005$) were greater for EVLA than for foam (EQ-5D, $p = 0.004$). There were fewer procedural complications in the EVLA group (1%) than after foam (7%) and surgery (8%) ($p < 0.001$). Participants returned to a wide range of behaviours more quickly following foam or EVLA than following surgery ($p < 0.05$). There were no differences in VCSS between the three treatments. Truncal ablation rates were higher for surgery ($p < 0.001$) and EVLA ($p < 0.001$) than for foam, and were similar for surgery and EVLA.

Conclusions: Considerations of both the 6-month clinical outcomes and the estimated 5-year cost-effectiveness suggest that EVLA should be considered as the treatment of choice for suitable patients.

Future work: Five-year trial results are currently being evaluated to compare the cost-effectiveness of foam, surgery and EVLA, and to determine the recurrence rates following each treatment. This trial has highlighted the need for long-term outcome data from RCTs on QoL, recurrence rates and costs for foam sclerotherapy and other endovenous techniques compared against each other and against surgery.

Trial registration: Current Controlled Trials ISRCTN51995477.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 19, No. 27. See the NIHR Journals Library website for further project information.

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List of abbreviations

ARI	Aberdeen Royal Infirmary
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	body mass index
BRAVVO	Behavioural Recovery After treatment for Varicose Veins
CEAC	cost-effectiveness acceptability curve
CEAP	clinical, etiological, anatomical, pathological
CHaRT	Centre for Healthcare Randomised Trials
CI	confidence interval
CIVIQ	Chronic Venous Insufficiency Quality of Life Questionnaire
CLASS	Comparison of LAser, Surgery and foam Sclerotherapy
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CS-SRM	common-sense self-regulation model
CTA	clinical trial authorisation
DMC	Data Monitoring Committee
DVT	deep-vein thrombosis
ECG	electrocardiograph
EQ-5D	European Quality of Life-5 Dimensions
EVLA	endovenous laser ablation
GLM	generalised linear model
GP	general practitioner
GSV	great saphenous vein
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICF	International Classification of Disability and Function
IMP	investigational medicinal product
IPQ-R	Illness Perception Questionnaire – Revised
MHRA	Medicines and Healthcare Products Regulatory Agency
MNAR	missing not at random
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
OC	oral contraceptive
OLS	ordinary least squares
OR	odds ratio
PIL	patient information leaflet
PROM	patient-reported outcome measure
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
Rc	ceiling ratio
RCT	randomised controlled trial
RFA	radiofrequency ablation
SAE	serious adverse event
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-36	Short Form questionnaire-36 items
SFJ	saphenofemoral junction

SSV	small saphenous vein	VAS	visual analogue scale
STS	sodium tetradecyl sulphate	VCSS	Venous Clinical Severity Score
TSC	Trial Steering Committee	WTP	willingness to pay

Plain English summary

Many people undergo treatment for varicose veins, which are visible tortuous veins. Different types of treatment are available. These are surgery (that is, removing the vein by stripping it out), laser (using the heat energy of the laser to close the vein) or injection of a foam to make the walls of the vein stick together.

We compared these three treatments in terms of how well they worked from a participant and clinician perspective and their relative cost-effectiveness. Seven hundred and ninety-eight people with varicose veins requiring treatment were allocated at random to one of these three treatments. Outcomes were assessed at 6 weeks and 6 months. We found that all three treatments reduced the symptoms associated with varicose veins and improved quality of life (QoL). Foam allowed people to return to their normal activities quickly, but had fewer benefits in terms of patient-reported QoL and more complications.

Foam was also less likely to close the leaky vein, thus increasing the chance of more treatment being needed in the future. Overall, the main finding is that consideration of both success at 6 months and estimated 5-year costs and benefits suggests that laser should be considered as the preferred treatment for patients who are suitable for all three treatment options. We are following the study participants to 5 years, as long-term results are important to determine the longer-term costs and consequences (in terms of recurrent varicose veins) of these three treatments.

Scientific summary

Background

The treatment of patients with varicose veins imposes a considerable workload and financial burden on the NHS. Foam sclerotherapy (foam) and endovenous laser ablation (EVLA) have emerged as alternative treatments to surgery for patients with varicose veins, but uncertainty exists regarding their clinical effectiveness and cost-effectiveness in the medium and long term. In particular, the rate of recurrence of varicose veins is unclear. If this is greater than after conventional surgery, then the potential short-term gains of minimally invasive therapy may be lost by the need for additional treatment.

Aims and objectives

Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) is a pragmatic, parallel-group randomised controlled trial (RCT) designed primarily to assess the clinical effectiveness and cost-effectiveness of three treatment modalities: (a) foam; (b) EVLA (with delayed foam sclerotherapy to residual varicosities when required); and (c) surgery.

Primary outcome measures included disease-specific quality of life (QoL), measured by the Aberdeen Varicose Vein Questionnaire (AVVQ), and generic QoL, measured by the European Quality of Life-5 Dimensions (EQ-5D) and Short Form questionnaire-36 items (SF-36) physical and mental component scores at 6 months (and 5 years), as well as cost-effectiveness, measured as cost per quality-adjusted life-year (QALY) gained.

The secondary objective was to compare the three treatments for (a) clinical success, as determined by residual varicose veins, Venous Clinical Severity Score (VCSS), complication rates and return to normal activities; (b) QoL [AVVQ, SF-36 physical and mental components and domains, EQ-5D and EQ-5D visual analogue scale (VAS) at 6 weeks, and SF-36 domains and EQ-5D VAS at 6 months]; (c) anatomical success, determined by duplex scan [partial or complete ablation of, or the presence of reflux in, the great saphenous vein (GSV) or small saphenous vein (SSV)] at 6 months; and (d) the cost to the health service and to patients of each intervention and any subsequent care.

Methods

Seven hundred and ninety-eight patients referred from primary care to vascular surgery departments in 11 UK centres for treatment of their varicose veins were recruited over 48 months (between November 2008 and October 2012). Research ethical approval and full written informed consent were obtained. The trial involved an off-licensed use of a licensed product, sodium tetradecyl sulphate (STS) (Fibrovein®, STD Pharmaceutical), for which Medicines and Healthcare Products Regulatory Agency (MHRA) approval was obtained.

We included adult patients with primary varicose veins which were symptomatic [clinical, etiological, anatomical, pathological (CEAP) classification C2 grade or above], either unilateral or bilateral, and those with GSV and SSV with reflux > 1 second on duplex ultrasound. We excluded those with current deep-vein thrombosis or acute superficial-vein thrombosis; GSV or SSV < 3 mm or > 15 mm in diameter; tortuous veins that were considered to be unsuitable for EVLA; and contraindications to foam or to general/regional anaesthesia which would be required for surgery.

Study set-up

Patients were randomised within two strata: stratum A included eight hospitals which offered all three treatment options and stratum B included three hospitals which offered only two treatment options (foam sclerotherapy and surgery). Outcomes were assessed at 6 weeks and 6 months post treatment. At 6 weeks, patients in the foam and EVLA arms were offered foam for any residual varicosities.

Randomisation

Participants were randomised using a computer-generated randomisation system managed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen. Participants were randomly allocated 1 : 1 to all the options available at each site. The minimisation algorithm included centre, age (< 50 years, ≥ 50 years), sex, presence of GSV or SSV reflux and unilateral or bilateral varicose veins.

Study interventions

Surgery of the main truncal veins and varicose tributaries was performed concurrently. EVLA of the main truncal veins was performed at an initial treatment, with foam to residual varicosities, if required, carried out at or after 6 weeks. For foam, 3% STS was administered to truncal and 1% to non-truncal veins. Foam to non-truncal varicosities was performed in 31% of patients following EVLA and in 38% randomised to foam.

Statistical analysis

An intention-to-treat analysis was performed. The primary and secondary outcomes were compared using mixed linear repeated-measures models, adjusting for baseline covariates. For secondary outcomes, a p-value > 0.005 was considered to be non-definitive. A trial-based cost-effectiveness analysis assessed mean differences in costs and QALYs at 6 months, and estimates of cost-effectiveness were extrapolated to 5 and 10 years using a Markov model. Estimates of cost-effectiveness were expressed as incremental costs per QALY gained, and the net monetary benefit (NMB) approach was used to identify the optimal treatment modality on grounds of cost-effectiveness, based on a ceiling willingness-to-pay (WTP) ratio of £20,000 per QALY gained.

The original trial sample size of 1015 (surgery vs. foam: 90% power, 5% significance; EVLA vs. foam or surgery: 80% power, 5% significance) was revised to 779 based on data which showed that the correlation between AVVQ at baseline and 6 months was better than originally assumed. We did not revise our original, minimally clinically important difference.

Results

In total, 6592 patients who attended outpatient clinics with varicose veins were unselectively screened for eligibility, and of these 3369 (51%) met the eligibility criteria. Of those who were ineligible, 43% did not fulfil the criteria for treatment in the NHS because they were asymptomatic, had no reflux, or had concurrent comorbidities or current thrombosis. A further 28% of patients had recurrent varicose veins. Less than 20% were excluded because the vein diameter was too small, too large or too tortuous. Of the 3369 eligible patients, 798 (24%) consented to participate in the trial and 76% (2571 patients) declined. The majority (78%) of patients who were eligible but declined participation did so because they had a preference for a particular treatment. Of the 798 patients who were recruited, 13 (1.6%) were excluded after randomisation. Seven hundred and twenty (92%) received their allocated treatment, 27 (3%) received a study treatment other than their randomised treatment and 38 (5%) did not receive any of the study treatments. Seven hundred and nine (90%) patients attended for the 6-weeks follow-up appointment and 670 (85%) completed the 6-weeks questionnaire. Six hundred and seventy (85%) patients attended for the 6-months follow-up appointment and 627 (80%) completed the 6-months questionnaire.

Quality of life

Aberdeen Varicose Vein Questionnaire

In all groups, disease-specific AVVQ scores improved over time (i.e. scores reduced). In the foam versus surgery comparison, the health gain obtained in the AVVQ was lower in patients undergoing foam [6 weeks $p = 0.002$; at 6 months, effect size −1.74, 95% confidence interval (CI) −2.97 to −0.50; $p = 0.006$]. EVLA and surgery had similar health gains in the AVVQ. The health gain for AVVQ in the foam versus EVLA comparison was similar at 6 weeks and 6 months.

European Quality of Life-5 Dimensions

There were no differences in the EQ-5D and EQ-5D VAS in the surgery versus EVLA or surgery versus foam comparisons at 6 weeks or 6 months. There was a significantly greater health gain at 6 weeks in patients who underwent EVLA than in those in the foam group in the EQ-5D ($p = 0.004$), but not in the EQ-5D VAS. There were no differences at 6 months.

Short Form questionnaire-36 items

There were no differences between surgery and foam for the overall physical and mental component scores or in the surgery versus EVLA comparison. In the comparison of EVLA versus foam, there were no differences in the SF-36 physical or mental component scores at 6 weeks or the SF-36 physical component at 6 months. At 6 months, the health gain in the SF-36 mental component was greater for EVLA than for foam (effect size 1.54, 95% CI 0.01 to 3.06; $p = 0.048$).

Cost-effectiveness

At 6 months, foam sclerotherapy was the least costly option, followed by EVLA and then surgery. Based on consideration of costs and QALYs at 6 months, foam had the highest probability of being considered cost-effective at a ceiling WTP ratio of £20,000 per QALY. A sensitivity analysis showed that EVLA would generate the greatest NMB at this threshold at 6 months, but only if performed in a clinic setting, rather than in an operating theatre.

The cost and effect data from the trial were used to populate a 5-year Markov cost-effectiveness model. For the first 6-month cycle, the model was populated using mean cost and utility data obtained from all randomised patients. Beyond 6 months, the best available evidence on the risk of clinical recurrence following each treatment modality was used to model clinical recurrence and subsequent associated costs and consequences. The model suggests that, for patients considered clinically suitable for all three treatment options, EVLA had the highest probability (≈ 79%) of being cost-effective at 5 years when applying a ceiling ratio of £20,000 per QALY gained, followed by foam (≈ 17%) and then surgery (≈ 5%). In a two-way comparison between foam and surgery, surgery was found to have the greatest probability of being cost-effective at 5 years, although a great deal of uncertainty surrounds this finding owing to the significantly higher cost of surgery and lack of long-term recurrence rates data for both interventions.

Clinical outcomes

At 6 months there were no differences in the VCSS between treatment groups. There were fewer residual veins at 6-months follow-up (lower VAS scores) in the surgery group than in the foam group (nurse- and patient-reported data, $p < 0.001$). Fewer patient-reported residual varicosities were noted in the EVLA group than in the foam group at 6 months ($p = 0.005$).

Ablation rates

At 6 months, both surgery ($p < 0.001$) and EVLA ($p < 0.01$) were more effective than foam. There were no differences between EVLA and surgery.

Complications

The event rate for any procedural complication was similar for surgery and foam (7% for surgery and 6% for foam), but at 6 months complications were significantly more frequent after foam than after surgery ($p < 0.05$). Complications which occurred less frequently after surgery than after foam were lumpiness (6 weeks and 6 months, $p < 0.001$), skin staining (6 weeks, $p < 0.001$; 6 months, $p < 0.001$), persistent tenderness (6 weeks, $p < 0.001$) and headache (6 weeks, $p = 0.047$). Cutaneous numbness was more common after surgery than after foam, at 6 weeks and 6 months ($p < 0.001$).

The event rate for any procedural complication was lower for EVLA (1%) than for either foam (7%) or surgery (8%) ($p < 0.001$). At 6 weeks, the following occurred less frequently in patients undergoing EVLA than in those undergoing foam: persistent bruising ($p < 0.001$), persistent tenderness ($p < 0.001$), lumpiness ($p < 0.001$) and skin staining ($p < 0.001$). Cutaneous numbness occurred more frequently following EVLA than following foam (6 months, $p = 0.012$).

In the surgery versus EVLA comparison, persistent bruising ($p = 0.012$), persistent tenderness ($p = 0.011$) and lumpiness ($p = 0.018$) occurred more frequently in patients undergoing surgery at 6 weeks, whereas lumpiness ($p = 0.041$) and skin staining ($p = 0.009$) were less frequent after surgery at 6 months. Finally, cutaneous numbness was less common after EVLA than after surgery ($p = 0.037$) at 6 months.

Behavioural recovery

We developed an instrument, BRAVVO (Behavioural Recovery After treatment for Varicose Veins), in order to (a) identify which behaviours are important to patients when recovering from varicose vein treatment, and (b) measure how quickly patients return to performing these activities after treatment. Results showed that patients were able to return to a wide range of behaviours more quickly following foam and EVLA than after surgery.

Conclusions

This is the first RCT involving foam to evaluate disease-specific QoL as a primary outcome measure. It shows that the health gain achieved with foam (AVVQ) was significantly lower than that for surgery at 6-months follow-up. No differences were noted between surgery and foam in the other QoL outcome measures. EVLA was marginally superior to foam in terms of the SF-36 mental component, but there were no differences in the other QoL measures at 6 months. EVLA and surgery were broadly equivalent in terms of QoL at 6 months. Greater gains in QoL were observed for EVLA at 6 weeks than for surgery, and for surgery and EVLA than for foam. Foam sclerotherapy produced the greatest NMB at 6 months, at a ceiling WTP ratio of £20,000 per QALY gained. Markov modelling, based on the trial data and the limited data currently available on longer-term recurrence rates, suggested that, at 5 years, EVLA is most likely to be the treatment of choice for suitable patients, based on considerations of both clinical effectiveness and cost-effectiveness. In a two-way comparison between foam and surgery, we found surgery to have the higher probability of being cost-effective at 5 years.

The presence of residual varicose veins and the frequencies of some complications were higher after foam than after either surgery or EVLA. This may have had an impact on QoL. However, participants returned to normal activities more quickly following foam than following EVLA or surgery. Truncal vein ablation rates were independently assessed and were found to be significantly lower in the foam group than in the surgery and EVLA groups. The reduced ablation rates observed for foam may lead to an increased risk of developing recurrent varicose veins in those patients, with associated reduced QoL and costs of further treatment. However, the 5-year recurrence rates following foam are unknown.

Strengths and weakness

The study experienced recruitment difficulties which led to a revision in the target size based on an interim analysis. This did not lead to any reduction in the predefined clinically important difference in QoL, but may have disadvantaged the EVLA arm, which had reduced power.

Following an unselected screening process, 43% of patients were found to be ineligible for randomisation. Of these, 30% were excluded because they would not be offered treatment in the NHS (i.e. they were asymptomatic, had no truncal reflux or had current thrombosis) and a further 28% had recurrent varicose veins. Less than 20% were excluded because the vein diameter was too small or large, or too tortuous. Thus, the results appear generalisable to the majority of patients undergoing treatment of primary varicose veins in the NHS.

Despite the fact that many eligible patients chose not to take part, those who did appear broadly similar to those in other RCTs, with the exception that there was a lower-than-expected proportion of females. The CEAP classification grade, VCSS (pre/post treatment) and QoL (pre/post treatment) were similar to those in other RCTs. The QoL values were also similar to those published in NHS England patient-reported outcome measures. Although the complete success rates for the GSV are at the lower end of those published in other RCTs, many studies defined 'technical success' as the combination of complete ablation and partial success with no reflux. The overall 'technical success' rate for CLASS is comparable (91% for EVLA and 82% for surgery). The results for foam (67% complete and partial with no reflux) remain lower than in some studies, but are comparable with those of two RCTs.

Overall summary

We believe that the results of this trial are generalisable to patients with primary varicose veins who are suitable for treatment with EVLA, foam or surgery. Our results suggest that EVLA should be considered as the preferred option in terms of both clinical outcomes at 6 months and estimated 5-year cost-effectiveness.

Recommendations for future research

Long-term outcome data from RCTs on QoL, recurrence rates and costs are required for foam and other endovenous techniques, compared against each other and against surgery.

Trial registration

This trial is registered as ISRCTN51995477.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Health Technology Assessment-commissioned call

The original application for this study was submitted in 2006 in response to a Health Technology Assessment (HTA) programme-commissioned call (06/45) for studies involving foam sclerotherapy. The call specified a primary outcome of quality of life (QoL) at 6 months. As a result of this call, the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) trial was funded. This first chapter reflects the NHS practice and the evidence available at that time. The second chapter discusses changes in NHS practice and relevant literature published since 2006.

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.[1] This resulted in approximately 37,500 operations being performed in the year April 2005 to March 2006 in England alone.[2] Approximately 20% of these operations are for recurrent varicose veins.[3] Varicose veins may result in pain, discomfort, itchiness and skin changes.

Throughout the UK prior to 2006, there were considerable variations in access to treatment for uncomplicated varicose veins. This may have been due to a belief on the part of those commissioning services, and some vascular surgeons, that it was a cosmetic procedure.[4] This was based on the results of a community-based study which showed no relationship between the presence of varicose veins, reflux in the main truncal veins and symptoms.[5] However, several studies had shown that many patients with varicose veins had reduced QoL, which was improved following treatment.[6–9] A randomised controlled trial (RCT) of surgery versus conservative management of patients with uncomplicated varicose veins estimated that the incremental cost per quality-adjusted life-year (QALY) gained was £4682, with a 70% probability that the cost per QALY would be lower than the National Institute for Health and Care Excellence (NICE) threshold of £20,000.[10]

Treatment options

At that time, the established mainstay of treatment for incompetent varicose veins was surgery in the form of saphenofemoral junction (SFJ) ligation or small saphenous vein (SSV) ligation, stripping and multiple phlebectomies of non-trunk varicosities. Evidence at the time suggested a recurrence rate at 5 years for this kind of conventional surgery of 32% for great saphenous veins (GSVs) and 50% for small saphenous veins.[3]

From the time of their introduction around 2000, foam sclerotherapy, endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) had emerged as possible alternative treatment options that could be carried out under local anaesthetic. Foam sclerotherapy, EVLA and RFA aim to reduce the surgical trauma, bruising, scarring and time off work associated with conventional surgery. By 2006, NICE had published interventional procedures guidance on all these procedures, stating that there was adequate evidence on their safety and efficacy for use in the NHS.[11–13] These newer interventions had the potential to increase throughput of varicose vein patients without the need for expensive operating theatre facilities. However, this benefit may be offset by the need for the patient to return for further treatment.

In 2006, there were only two completed RCTs comparing the newer treatments against surgery, both with limited follow-up. One had been published,[14] whereas the other, carried out by one of the CLASS co-applicants, had not.[15] These studies are discussed below (see *Foam sclerotherapy* and *Endovenous laser ablation*). Critics of the newer procedures pointed to the unknown effect of not treating tributaries at the

saphenopopliteal junction and SFJ (an accepted principle of surgery aimed at minimising recurrence) and the need for several treatment sessions compared with 'one-stop' surgery.

Despite uncertainty about clinical effectiveness and cost-effectiveness, the use of these newer treatment options was increasing in the UK as alternatives to conventional surgery. A survey in 2006 of members of the Vascular Surgical Society of Great Britain and Ireland and the Venous Forum of the Royal Society of Medicine revealed that the vast majority of surgeons offered conventional surgery to NHS patients, with 27% of surgeons offering foam sclerotherapy, 19% offering EVLA and 3% offering RFA.[16] The following sections describe each of these treatments.

Foam sclerotherapy

Foam sclerotherapy is a development of conventional liquid sclerotherapy, aimed at more extensive and reliable ablation of veins through a process of chemical phlebitis. In 2006, use of foam sclerotherapy represented an 'off-licence' use of the licensed sclerosant. Several different liquid sclerosants of varying concentrations were being mixed with air to produce foam. The use of foam rather than the liquid sclerosant allows increased contact with the endothelium, and less mixing and dilution with venous blood. However, the foam could vary in consistency, which may affect efficacy.[17] Foam sclerotherapy induces irritation of the endothelium, leading to thrombosis.

A systematic review of the safety and efficacy of foam found that foam appeared efficacious in terms of obliterating the main trunk veins,[18] but more than one treatment session may be required to achieve this. In a series of 500 patients, Cabrera[19] achieved obliteration of the GSV in 81% of cases; 86% of patients achieved this after one injection, while 11% required two injections and 4% required a third. Other published data indicated that only 43% of patients undergoing foam sclerotherapy were adequately treated in a single treatment, with 48% requiring two sessions and 9% more sessions.[20] Across the studies included in the review, the median rate of recurrence or development of new varicose veins up to 10 years ranged from 3% to 28%, but the risk of recurrence or development of new veins was not significantly different to that of comparator treatments.[18] The authors concluded that there was insufficient evidence to compare the effectiveness of foam sclerotherapy reliably with other minimally invasive therapies or surgery.[18]

In 2006, there was only one RCT of a commercial preparation for foam sclerotherapy [Varisolve® polidocanol microfoam (BTG International, London, UK)], which was a licensed product in which sclerosant was mixed with gas (oxygen and carbon dioxide). This was a three-arm study of 710 patients, which compared Varisolve® against either sclerotherapy (liquid or investigator-generated foam) or conventional surgery (ligation and stripping of the GSV).[14] No differences were detected in the primary outcome of technical success (ablation of the GSV) at 3 months. At 12 months, technical success was slightly higher in the surgery than in the Varisolve® group (86% vs. 79%, $p = 0.11$). Following Varisolve® foam sclerotherapy, patients required a median of 2 days to return to 'normal activities' compared with 13 days following surgery. QoL was not assessed. No RCTs were identified comparing foam sclerotherapy with EVLA.

The main safety concern regarding foam sclerotherapy was the potential for the foam to enter the deep venous system, with the risk of deep-vein thrombosis (DVT), and also to enter the systemic circulation, so reaching the heart and possibly the eye or brain via an atrial septal defect, which is present in 25% of the population. As a result, the NICE guidance for foam sclerotherapy recommended special arrangements for consent, audit and research,[13] and limits were recommended on the amount of foam injected per session,[21] necessitating additional treatment sessions to deal with non-truncal varicosities. In the systematic review, the incidence of DVT following treatment varied from 0.3% to 3%, while transient visual disturbance occurred in up to 2.8% of patients and transient ischaemic attack in 0% to 0.3% of patients.[18] The review reported one case of ischaemic stroke occurring immediately after injection, with partial recovery at 3 months; this occurred in a patient with a patent foramen ovale.[18] Other potential adverse events include thrombophlebitis (15–58%); early skin discolouration over the treated vein (11–50%); skin necrosis (0.01–0.9%); ulceration (0–7%); and allergy (0.3%).[18]

Endovenous laser ablation

Endovenous laser ablation results in thermal ablation of the truncal veins. Most studies describing EVLA had used either 810- or 940-nm diode lasers based on a haemoglobin absorption peak to red/infrared light of 800–1000 nm.[22] The heat generated by the laser was believed to result in thermal damage to the endothelium and subendothelial layer, resulting in focal coagulative necrosis and shrinkage and leading to thrombotic occlusion of the vein.[23] 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.[24] Studies had shown that between 30% and 99% of patients receiving EVLA require subsequent treatment for non-trunk varicosities.[22]

It had been shown that successful occlusion was dependent on the energy used and could be achieved in all veins treated with ≥ 70 J/cm.[25] A RCT carried out by one of the CLASS co-investigators reported on 118 patients randomised to EVLA or surgery.[15] At 3-months follow-up, abolition of reflux was achieved in 98% of EVLA and 92% of surgical patients. EVLA patients had a quicker return to normal activities and work ($p = 0.01$). Improvements in the Aberdeen Varicose Vein Questionnaire (AVVQ) score, a disease-specific quality of life instrument, were similar in both groups. At 1 year follow-up, there was recanalisation in a minority of the EVLA-treated GSVs, but SFJ reflux remained abolished in 86% of patients who were available for follow-up.

A systematic review[26] assessed the effectiveness and safety of EVLA in 13 case series involving 1289 patients (1631 limbs) with duplex-proven primary venous reflux; the mean length of follow-up ranged from 1 to 19 months. EVLA was effective in the short term, with occlusion of the GSV occurring in 88–100% of limbs. Mundy *et al.*[26] 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 DVT. Other reported complications of EVLA included superficial laser burns in 5% of patients in one study which used a very high laser energy; ecchymosis or skin discolouration (23–100% of limbs), which was generally self limiting; phlebitis in 1.6% of limbs; and saphenous paraesthesia in 1–36.5% of limbs.[26] The Australian Medical Services Advisory Committee, in its 2003 assessment report, concluded that EVLA and conventional surgery were similar in terms of safety.[27]

The Comparison of LAser, Surgery and foam Sclerotherapy trial

It was against this background of continuing uncertainty about the relative clinical effectiveness and cost-effectiveness of foam sclerotherapy compared with surgery that the National Institute for Health Research (NIHR) HTA programme commissioned a call and the CLASS trial was funded. The CLASS trial was an 11-centre, three-arm comparison of foam sclerotherapy, EVLA and surgery, comparing the relative clinical effectiveness and cost-effectiveness of the three procedures. We chose to include EVLA in addition to foam sclerotherapy in our application because EVLA and foam were the most commonly used minimally invasive treatment options within the NHS at that time. We did not include RFA as, at the time of applying for funding, this technique was more costly and less suited to local anaesthesia on account of the contact time required between the probe and vein endothelium. However, developments since then have made RFA faster and suitable to be performed under a local anaesthetic. EVLA and RFA are now considered to be comparable techniques in terms of outcome.[28]

Since the start of the CLASS trial, a further five RCTs comparing foam sclerotherapy against surgery and/or EVLA have been published,[29–33] and also 10 RCTs which have compared EVLA against surgery.[15,29,31,34–40] These, and relevant changes in NHS practice regarding the treatment of varicose veins, are reviewed in *Chapter 2*. Despite these new studies, the 2013 NICE guidelines on the management of varicose veins found that the evidence comparing conventional surgery with foam sclerotherapy or with endovenous thermal ablation was of low quality.[28]

The structure of the remainder of the monograph is as follows. *Chapter 3* describes the methodology underpinning the CLASS trial. In *Chapter 4* we describe the trial participants. *Chapters 5* and *6* present the clinical effectiveness results up to 6 months. In *Chapter 7*, we discuss the clinical effectiveness results. *Chapter 8* describes the development of an instrument to assess return to normal activity in terms of behavioural recovery and the trial results in terms of this outcome. *Chapter 9* presents the within-trial cost-effectiveness analysis. In *Chapter 10*, we present economic modelling beyond the 6-month follow-up period. Finally, the overall results of the study are discussed in *Chapter 11*, together with implications for practice and recommendations for future research.

Chapter 2 Changes in practice and literature update

Recent changes in practice

Since the start of the CLASS trial, several surveys have shown an increased use of newer endovenous treatment options in the NHS.[16,41,42] Since 2006, specific codes for the minimally invasive treatment options have been introduced and Hospital Episode Statistics have shown that the most commonly used minimally invasive treatment is foam sclerotherapy, followed by EVLA.[43] However, overall, 70% of those having treatment of varicose veins in the NHS still undergo surgery.[43]

Quality of life as an outcome measure has become increasingly important; the standard NHS contract for acute services in England requires that all licensed providers of NHS-funded varicose vein procedures ask patients to complete patient-reported outcome measure (PROM) questionnaires before and after surgery. This includes the disease-specific AVVQ, the generic European Quality of Life-5 Dimensions (EQ-5D) index and EQ-5D visual analogue scale (VAS). The PROMs data have shown that varicose vein treatment results in significant improvement in health for patients, with over 80% experiencing an improvement in the AVVQ and almost a 50% reduction in the AVVQ score from pre-operative values.[44] Despite this clear benefit, the number of varicose vein treatments being performed in the NHS has fallen (from approximately 36,650 in 2009–10[28] to approximately 27,600 in 2011–12[2]) owing to rationing of treatment, as a result of restrictions in referrals from primary to secondary care.

Literature update: randomised controlled trials of foam sclerotherapy alone versus surgery or endovenous treatments

EMBASE (1980 to week 37, 2012), Ovid MEDLINE (1946 to September week 2, 2012) and Ovid MEDLINE In-Process & Other Non-Indexed Citations were searched using terms designed to identify randomised comparisons of foam sclerotherapy, surgery and EVLA. In addition, the HTA database, Database of Abstracts of Reviews of Effects (DARE) and Cochrane Database of Systematic Reviews (CDSR) were searched using similar terms. Identified abstracts were screened for relevant papers. All searches were updated in 2013. In addition, the reference lists of identified papers were searched for any relevant papers.

At the time of submitting the proposal, there was only one RCT in which foam sclerotherapy was compared against surgery;[14] by mid-2013 a further five RCTs had been published comparing foam sclerotherapy with surgery and/or thermal ablation (*Table 1*).[29,30–33] All these studies involved treatment to the GSV only. In two, foam sclerotherapy with concomitant phlebectomies was compared with EVLA.[29,32] The outcome of these studies in terms of QoL, technical success, return to normal activities, Venous Clinical Severity Scores (VCSSs), recurrence rates and costs are discussed below.

In addition, there are four further RCTs which have compared foam sclerotherapy of the GSV with ligation of the SFJ against conventional surgery.[45–48] These are not discussed further because ligation of the SFJ is not considered minimally invasive treatment, and therefore its use with foam undermines the value of foam as a simple, minimally invasive treatment option. In addition, this type of treatment is not one which has been adopted in UK practice.

TABLE 1 Randomised controlled trials of foam sclerotherapy (alone) vs. conventional surgery or EVLA for the treatment of primary varicose veins

Study	Number of patients, centres, vein involvement	Comparators[a]	Primary outcomes	Other outcomes
Biemans 2013[31]	233, single centre, GSV	Foam sclerotherapy vs. EVLA vs. surgery	Anatomical success at 1, 3 and 12 months, post-operative neovascularisation	CEAP classification, complications, QoL (CIVIQ, EQ-5D)
Lattimer 2012[32]	100, single centre, GSV	Foam sclerotherapy with phlebectomies vs. EVLA with phlebectomies	Technical success at 3 months	Cost, VCSS, QoL (AVVQ) up to 3 months, return to normal activities
Shadid 2012[33]	460, three hospital sites, GSV	Foam sclerotherapy with delayed phlebectomies or further foam sclerotherapy vs. surgical stripping with high ligation	2-year recurrence, defined as reflux combined with venous symptoms	Recurrent reflux, symptoms, QoL (EQ-5D), adverse events, direct hospital costs up to 2 years
Rasmussen 2011[29]	500, two centres, GSV	Foam sclerotherapy with phlebectomies vs. EVLA, RFA or surgery	Technical success at 1 year (GSV closure)	Pain, absence from work and normal activity, QoL (AVVQ, SF-36), VCSS, recurrence rates up to 1 year
Figueiredo 2009[30]	60, single centre, GSV and SSV	Foam sclerotherapy vs. surgery with phlebectomy	VCSS up to 6 months	Technical success at 6 months, treatment complications
Wright 2006[14]	710, multicentre, GSV and SSV	Foam sclerotherapy (manufactured foam: Varisolve®) vs. surgery or sclerotherapy (liquid or investigator-generated foam)	Technical success at 3 months	Technical success at 12 months, return to normal activities

CEAP, clinical, etiological, anatomical, pathological; CIVIQ, Chronic Venous Insufficiency Quality of Life Questionnaire; SF-36, Short Form questionnaire-36 items; VCSS, Venous Clinical Severity Score.
a In studies where surgery was the comparator, this involved high tie, stripping and phlebectomies.

Quality of life

Quality of life was assessed in four of the above studies. In the study by Biemans *et al.*,[31] there was no difference in QoL [assessed by the disease-specific Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) or the EQ-5D] at 3 months or 1 year. At 3 months, there was no significant difference in AVVQ scores between treatment groups.[32] At 1 year, Rasmussen *et al.*[29] found significant improvements in the AVVQ and Short Form questionnaire-36 items (SF-36) scores in all treatment groups, but no difference between any of the treatment groups. Similarly, Shadid *et al.*[33] found no significant difference in the EQ-5D scores between treatment groups at 2 years.

Technical success

This was assessed in all six studies at various time points up to 2 years. At 1 year, the occlusion rate for foam sclerotherapy (73%) was significantly lower than for either surgery (88%, $p < 0.02$) or EVLA (89%, $p < 0.02$).[31] At 3 months, the technical success rate was found to be similar for foam sclerotherapy and EVLA (above-knee GSV occlusion rate 69% vs. 74%, $p = 0.596$).[32] At 6 months, Figueiredo *et al.*[30] found no statistically significant difference in technical success between patients randomised to foam sclerotherapy and those randomised to surgery (vein obliteration in 90% vs. 78%).

In the study by Wright *et al.*,[14] the technical success at 12 months was slightly higher in the surgery group (86%) than in the Varisolve® group (84%), but this did not reach statistical significance. Rasmussen *et al.*[29] found that the technical success rates at 12 months were significantly lower in patients receiving foam (84%) than in those receiving EVLA (94%), RFA (95%) and surgery (97%) (χ^2 $p < 0.001$).

Duplex findings at medium-term follow-up

This has been assessed by Shadid *et al.*,[33] who found the presence of reflux to be greater in patients treated with foam sclerotherapy than in those receiving surgery at 2-year follow-up (35% vs. 21%, $p = 0.003$).

Return to normal activities

This was reported in three of the five studies. Wright *et al.*[14] found that the time to return to normal activities following treatment was shorter in the foam sclerotherapy group than in the surgical group (median 2 vs. 13 days, $p < 0.001$). In the study by Rasmussen *et al.*,[29] the median time to return to normal activities was shorter in the patients in the foam sclerotherapy and RFA groups (1 day in each) than in the EVLA (2 days) and surgery (4 days) groups ($p < 0.001$). The study by Lattimer *et al.*[32] found that the mean time to return to normal activities was shorter following foam (3 days) than EVLA (7.5 days) ($p = 0.11$).

Venous Clinical Severity Scores

The VCSSs were assessed in three studies, and improved significantly after the procedure in all groups, with no differences noted between groups.[29,30,32]

Clinical, etiological, anatomical, pathological classification

One study considered the clinical, etiological, anatomical, pathological (CEAP) classification.[31] Although the CEAP classification improved after foam sclerotherapy, EVLA and surgery, there was no difference between groups at 3 or 12 months.

Clinical recurrence rates

In the study by Rasmussen *et al.*,[29] the 1-year clinical recurrence rates in those randomised to foam, surgery, EVLA and RFA were similar (14%, 15%, 12% and 7% respectively, $p = 0.155$).

A further study defined clinical recurrence in terms of a combined end point of reflux combined with venous symptoms at 2 years.[33] This end point was found to occur equally in patients randomised to foam sclerotherapy (11%) or surgery (9%) ($p = 0.407$).

Costs

These were reported in three of the studies, with all three reporting that foam was the least costly option. Lattimer *et al.*[32] calculated the cost of foam sclerotherapy to be approximately one-third of the cost of EVLA. In the study by Shadid *et al.*,[33] hospital costs over a 2-year period in patients receiving foam sclerotherapy were less than half of those in the surgery group. Rasmussen *et al.*[29] found that foam sclerotherapy was the cheapest option, and that EVLA and surgery were more expensive.

Literature update: randomised controlled trials comparing endovenous laser ablation with surgery

At the time of submitting the proposal, there was only one completed (but unpublished) RCT in which EVLA was compared against surgery.[15] By mid-2013, a further eight RCTs had been published which compared EVLA against surgery of the GSV,[29,31,34–36,38–40,49–51] and one which compared EVLA against surgery to the SSV[37] (*Table 2*). Two of these studies[31,49] also included foam sclerotherapy; these are the only currently published studies which have compared foam sclerotherapy against EVLA. The outcomes of these studies in terms of QoL, technical success, return to normal activities, VCSS, recurrence rates and costs are discussed below.

TABLE 2 Randomised controlled trials of EVLA against conventional surgery

Study	Number of patients, centres, vein involvement	Comparators[a]	Primary outcomes	Other outcomes
Biemans 2013[31]	233, single centre, GSV	Foam sclerotherapy vs. EVLA vs. surgery	Anatomical success at 1, 3 and 12 months, post-operative neovascularisation	CEAP, complications, QoL (CIVIQ, EQ-5D)
Samuel 2013[37]	106, single centre, SSV	EVLA with phlebectomies vs. surgery	Technical success (abolition of reflux at 6 weeks)	Technical success, return to work and normal activities, complications, VCSS, QoL (AVVQ, EQ-5D, SF-36) up to 1 year
Rass 2012[38]	400, two centres, GSV	EVLA vs. surgery	Clinically recurrent varicose veins at 2 years	Duplex-detected saphenofemoral recurrence, QoL (CIVIQ), adverse events, clinical and functional outcome (HVVSS)
Flessenkamper 2012[39]	449, three centres, GSV	EVLA with phlebectomies ± high ligation vs. surgery	Venous reflux at proximal section of the GSV at 2 years (only 2-month data published)	Complications (including post-operative ecchymosis), CEAP
Carradice 2011[35,50]	280, single centre, GSV	EVLA with phlebectomies vs. surgery	QoL (SF-36)	Clinical recurrent varicose veins, duplex-detected reflux, technical success, VCSS, QoL (AVVQ, EQ-5D), return to work and normal activities
Rasmussen 2011[29]	500, two centres, GSV	EVLA with phlebectomies vs. foam, RFA or surgery	Technical success (GSV closure) at 1 year	Absence from work and normal activity, QoL (AVVQ, SF-36), VCSS, recurrence rates up to 1 year
Pronk 2010[40]	122, single centre, GSV	EVLA with delayed sclerotherapy vs. surgery	Clinical recurrence and technical success up to 12 months	Recovery, complications, CEAP
Christenson 2010[34]	200 limbs, single centre, GSV	EVLA vs. surgery	Duplex technical success at 2 years	VCSS, QoL (AVVQ, SF-36)
Darwood 2008[15]	118, single centre, GSV	EVLA with delayed foam sclerotherapy vs. surgery	Duplex technical success, QoL (AVVQ) at 3 months	Return to normal activity and work, technical success, QoL (AVVQ) at 1 year, VCSS
Rasmussen 2007,[36] 2010,[49] 2013[51]	121, two centres, GSV	EVLA with phlebectomies vs. surgery	Technical success, clinical recurrence at 6 months, 2 years and 5 years	VCSS, QoL (AVVQ, SF-36), costs

HVVSS, Homburg Varicose Vein Severity Score.
a In studies where surgery was the comparator, this involved high tie, stripping and phlebectomies.

Quality of life

Eight studies reported QoL, using instruments which included the AVVQ, SF-36, EQ-5D and the disease-specific CIVIQ. In all of these studies, no significant difference was noted in patients randomised to EVLA or surgery at various follow-up time points ranging from 3 months to 5 years.[15,29,31,34,35,37,38,50,51] Disease-specific QoL was found to be reduced in patients who developed a clinical recurrence compared with those who did not ($p = 0.001$).[35] In this study, the clinical recurrence rates were lower in patients who received EVLA than in those who underwent surgery at 1-year follow-up ($p < 0.001$).[35]

Technical success

This was assessed in all 10 of the studies at various time points. In the study by Flessenkamper *et al.*, technical success (no inguinal venous reflux) was achieved after 2 months in 92% of the EVLA group, 98% of the EVLA/high-tie group and 100% of the standard surgery group.[37,39] Darwood *et al.*[15] found that, at 3-months follow-up, abolition of reflux was achieved in 94% of EVLA and 88% of surgical patients ($p = 0.227$), and that, by 1 year, technical success had reduced in both groups. At 6 months, Rasmussen *et al.*[36] reported no significant difference in technical success at 1 year (94% in the EVLA group and 98% in the surgery group, $p > 0.05$). In the later study by Rasmussen *et al.*,[29] technical success was 94% following EVLA compared with 96% following surgery ($p = 0.543$). Biemans *et al.*[31] found no difference in anatomical success following EVLA (89%) or surgery (88%).

In the study by Carradice *et al.*,[35] the technical success rate at 6 weeks was slightly lower in patients randomised to surgery (92%) than in those who underwent EVLA (99%) ($p = 0.005$). In the study by Pronk *et al.*,[40] the technical success was similar in both surgery (90%) and EVLA (91%) groups at 1 year.

In the study by Christenson,[34] initial technical success (no detectable reflux at 12 days) was 99% in the EVLA group and 100% in the surgery group. The one study involving patients undergoing treatment to the SSV system found that the technical success (abolition of reflux) was greater in the EVLA group (96%) than in the surgery group (72%) at 6 weeks ($p < 0.001$).[37]

Duplex findings at medium-term follow-up

Over a 2-year follow-up, recanalisation (partial or complete) occurred in 7% of the EVLA group and none of the surgery group ($p = 0.051$).[34] Rass *et al.*[38] found that patients in the EVLA group had a higher rate of duplex-detected saphenofemoral reflux than those undergoing surgery at 2 years (18% vs. 1%, $p < 0.001$).

At 5 years, there was no difference in the proportion of open refluxing GSVs between EVLA (18%) and surgery groups (10%) ($p = 0.21$).[51]

Return to normal activities

In the study by Darwood,[15] patients randomised to EVLA had a quicker return to normal activities and work than those randomised to surgery ($p = 0.001$ and $p = 0.005$ respectively). Similarly, Rass *et al.*[38] found that patients having EVLA returned to work more quickly than those having surgery; this was despite there being no difference in return to basic physical activities between the groups. Pronk *et al.*[40] found that recovery (mobility, self-care and daily activities) was better in patients randomised to surgery than in those randomised to EVLA at day 7 ($p < 0.05$); however, there was no difference in the mean number of days taken to restart daily activities, work and sport between the groups. In two studies by Rasmussen *et al.*,[29,36] there was no difference in return to normal activities and work between patients randomised to EVLA and surgery. In the one study to involve patients undergoing SSV treatment,[37] patients who had EVLA returned to normal activities and work earlier than those undergoing surgery ($p < 0.001$).

Venous Clinical Severity Score

The VCSS was assessed in six studies, and scores improved significantly after treatment in all groups, with no differences noted between treatment groups.[15,29,34,37,49,51] In the study by Rass *et al.*,[38] an alternative assessment tool (the Homburg Varicose Vein Severity Score) was used; again there was no difference between treatment groups.

Clinical, etiological, anatomical, pathological classification

Three studies considered CEAP as an outcome measure. There was no difference in CEAP between intervention groups at 2 months[39] and 1 year[31,40] in patients undergoing EVLA versus surgery.

Clinical recurrence rates

These were reported in five studies. The clinical recurrence rates at 1 year, in the study by Pronk *et al.*,[40] were approximately 10% in both the EVLA and surgery groups. In contrast, Carradice *et al.*[35] found the clinical recurrence rate at 1 year to be lower after EVLA (4%) than after surgery (20%) ($p < 0.001$).

Rass *et al.*[38] reported recurrent varicose veins on clinical examination in 16.2% of the EVLA group versus 23.1% of the surgery group at 2 years ($p = 0.15$). Higher 2-year clinical recurrence rates were reported by Rasmussen *et al.*[49] (surgery 37%, EVLA 26%). In the 5-year results from this study, there was no difference in recurrence rates (surgery 55%, EVLA 47%, $p = 0.72$).[51] In the study by Rasmussen *et al.*[29] where four different treatment options were compared, clinical recurrence rates at 1 year were reported as 14% following foam, 15% following surgery, 12% following EVLA and 7% following RFA ($p = 0.155$).

Costs

In addition to the Rasmussen study,[29] which was discussed previously, the group has reported another study which assessed the costs of EVLA versus surgery.[36] In both studies, the procedure-related costs were higher for EVLA than for surgery.

Literature update: meta-analysis comparing foam with endovenous laser ablation and surgery (technical success, clinical recurrence rates and cost)

Treatment of recurrent varicose veins accounts for 20% of venous procedures in the NHS, and thus the long-term durability of any treatment is important both for the patient and for economic reasons. It is assumed that lower initial technical success rates will translate into higher clinical recurrence rates, reduced QoL, the need for further treatment and thus an increased cost to the NHS in the long term. The NICE meta-analysis of four studies comprising 966 randomised patients found that foam sclerotherapy was associated with a higher prevalence of reflux at 3–12 months (compared with conventional surgery), but there was not a large enough effect to show clear advantage for surgery.[28]

A meta-analysis of 72 predominantly observational studies (average follow-up 32 months) found that foam sclerotherapy was less effective than surgery in terms of technical success rates, and EVLA was more effective than surgery, foam sclerotherapy or RFA.[52] A further meta-analysis found that foam sclerotherapy was associated with a higher clinical recurrence rate in patients with GSV incompetence than the other newer treatments.[53]

A cost–utility analysis found that the incremental cost-effectiveness ratios (ICERs) at 5 years for foam sclerotherapy (vs. conservative care), EVLA (vs. foam sclerotherapy) and RFA (vs. EVLA) were £1366, £5799 and £17,350 per QALY respectively.[54] The ICER for conventional day-case surgery compared with RFA was £19,012. A further analysis undertaken by NICE found that endothermal treatment (i.e. EVLA or RFA) is the most cost-effective strategy, with an ICER of endothermal treatment compared with foam of £3161.[28] In both these analyses, the recurrence rate following the newer treatment options were based on estimates, owing to the lack of published data.

The systematic reviews and meta-analysis concluded that long-term data on clinical efficacy (particularly with regard to recurrence), QoL and costs are required from large high-quality prospective RCTs of foam sclerotherapy and other endovenous techniques, compared against each other and against surgery.[52,53,55,56]

Chapter 3 Trial design

In this chapter, we describe the aims and objectives of the CLASS trial, and the trial design. In presenting this information, we have followed the Consolidated Standards of Reporting Trials – patient-reported outcomes (CONSORT PRO) guidance.[57] We also provide the sample size calculation and describe the statistical analysis for the clinical effectiveness data. The methods for the cost-effectiveness and economic modelling chapters are contained within those individual chapters.

Aims and objectives

The primary objective of the CLASS trial was to compare the clinical effectiveness and cost-effectiveness of two minimally invasive treatment modalities performed under local anaesthetic – foam sclerotherapy of the main great or small saphenous truncal and non-truncal varicosities, and EVLA including delayed foam sclerotherapy of non-truncal varicosities – against surgery, in respect of disease-specific QoL (as measured by the AVVQ) and generic QoL (as measured by the EQ-5D and SF-36) for each intervention at 6 months (and ultimately to 5 years) and cost-effectiveness as cost per QALY gained.

Following discussion with the HTA programme, the primary outcomes were extended to involve an analysis of EVLA versus foam sclerotherapy. Thus, the study is a three-way comparison of foam sclerotherapy, EVLA and surgery. The 5-year results will be presented at a later stage.

The secondary objectives were to compare the two novel interventions against conventional surgery in respect of:

- clinical success, as determined by residual varicose veins, VCSS, 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 great or small saphenous trunk veins) at 6 months and any development of deep venous incompetence and neovascularisation
- the cost to the NHS and patients of each intervention and any subsequent care, including projected costs to 5 years, based on the 6-month costs via Markov modelling.

Overview of trial design

Comparison of LAser, Surgery and foam Sclerotherapy is a pragmatic, parallel-group trial designed to assess the clinical effectiveness and cost-effectiveness of (a) foam sclerotherapy of the main great or small saphenous trunk and non-trunk varicosities, and (b) EVLA of main truncal varicosities, including delayed foam sclerotherapy of non-trunk varicosities, when compared against surgery (the 'control' treatment). There were two strata; a recruitment site's placement in one or the other stratum depended on the treatment options available at that site. Stratum A included eight hospitals which offered all three treatment options; thus, participants recruited in hospitals in this stratum were randomised to one of the three interventions. Stratum B included three hospitals which offered two treatment options (foam sclerotherapy and surgery), and patients recruited in hospitals in this stratum were randomised to one of these interventions.

The trial design is detailed in *Figure 1*.

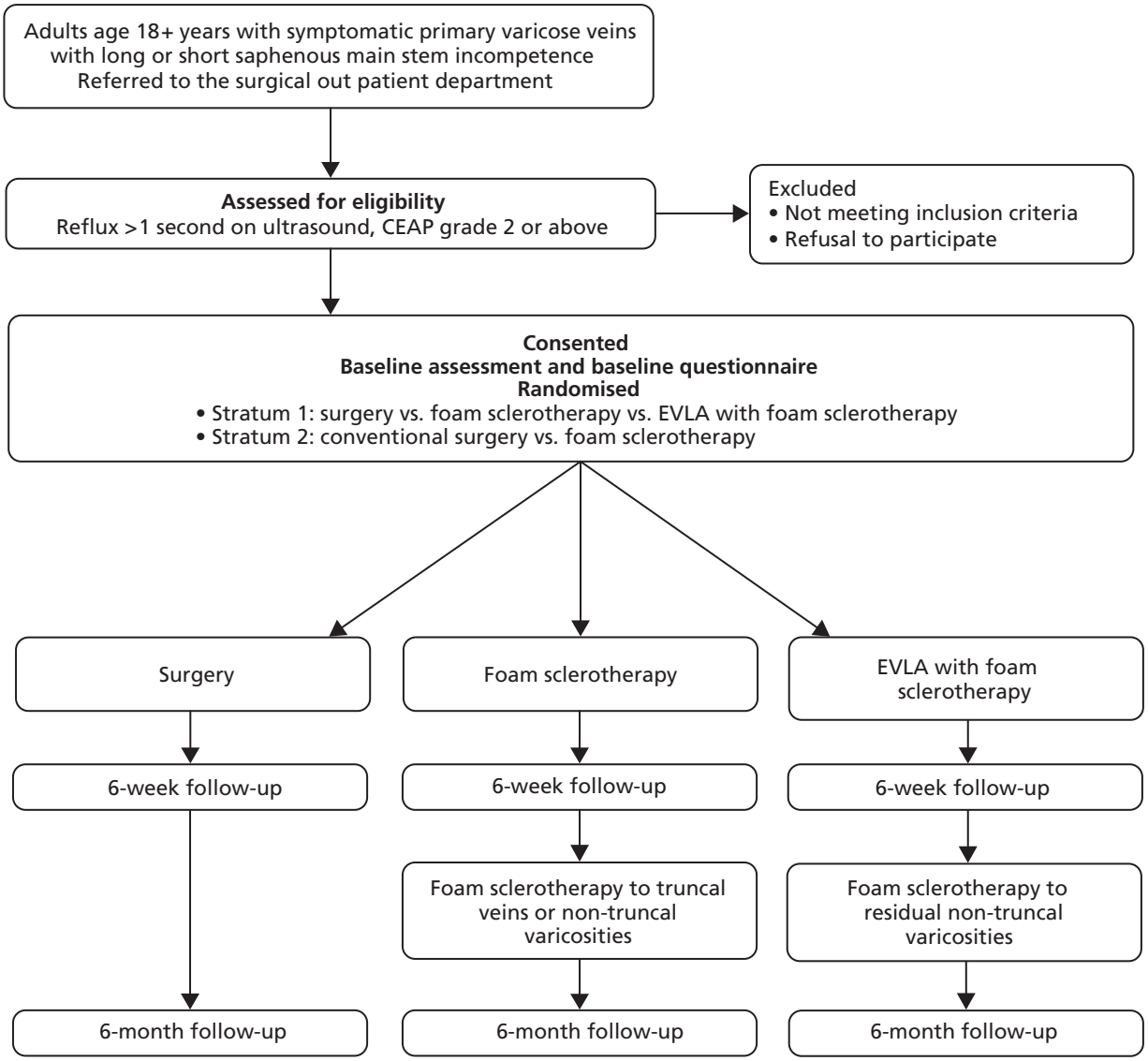

FIGURE 1 Overview of trial design.

Participants

Identification of patients

Patients referred from primary care to vascular surgery departments in 11 UK hospitals were identified by either a member of the clinical service or the local research nurse, and were recorded on the study log at each site.

Inclusion criteria

Adult patients (aged over 18 years) referred to the surgical outpatient department for treatment of primary varicose veins with symptomatic (CEAP grade 2 or above) great or small saphenous main truncal incompetence (reflux > 1 second on duplex scanning) were eligible for inclusion.

Exclusion criteria

The following exclusion criteria applied:

- current DVT, 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
- GSV or SSV < 3 mm in diameter or > 15 mm
- tortuous veins considered to be unsuitable for EVLA owing to difficulties in passing the guide wire
- inability to complete study questionnaires
- history of migraines which are frequent, or migraines which are severe enough to require hospitalisation
- other contraindications mentioned in the sodium tetradecyl sulphate (STS) (Fibrovein®, STD Pharmaceutical) prescribing information leaflet: varicosities caused by pelvic or abdominal tumours, cardiac failure, pulmonary oedema, local or systemic infection
- patients who were not fit for a general anaesthetic because of significant systemic disease, morbid obesity or other causes.

As all varicose vein treatments should be used with care in patients taking oral contraceptives (OCs) or hormonal replacement therapy (HRT), the surgeon either asked the patient to discontinue the OC or HRT prior to treatment or prescribed heparin prophylaxis therapy.

Recruitment process

In trial centres where potentially eligible patients could be identified in advance of their attendance at an outpatient clinic, the postal summary information sheet (see *Appendix 1*, which contains all study paperwork, case report forms and questionnaires) was sent to them in advance of their appointment. Patients who were identified at an outpatient clinic were provided with the summary information sheet at the clinic (see *Appendix 1*).

The surgeon informed potentially eligible patients about the CLASS study, the different treatments available and the risks and benefits of the treatment options. The surgeon also provided patients with a study information leaflet, and an information leaflet providing detailed information about the alternative methods of treatment.

In some centres, the duplex scan was undertaken during this initial consultation; in such cases, only those patients who were eligible on the basis of the results of this scan were informed about the study.

All patients attending an outpatient clinic were logged on the study clinic log. If the patient was potentially interested in the study, his or her contact details were noted on the study clinic log. For patients who were not eligible for the study, or who were not interested in taking part, we recorded the reason for this on the study clinic log.

Around 1 week after the initial consultation, the research nurse telephoned patients who had indicated that they were potentially interested in taking part in the trial to ascertain whether or not this was still the case. If the patient was interested in taking part in the study, he or she was invited to a recruitment appointment at the clinic to provide informed consent. If the patient did not undergo duplex scanning at the initial consultation, this was undertaken at the recruitment appointment. Participants were asked to complete a baseline questionnaire. The baseline case report form was also completed at this appointment.

In participants who presented with bilateral varicose veins, the more severely affected leg (as determined by the participant) was nominated as the study leg. Where possible, the other leg was treated using the same treatment modality as the study leg, either at the same time as the study leg was treated, or sometime thereafter.

In some circumstances (for example, where the duplex scan was completed at the initial consultation and the patient lived a considerable distance from the recruitment clinic, or it was difficult for him or her to attend a recruitment clinic), the consent form and baseline questionnaire were sent to the participant, who was asked to complete these and return them by post. In these circumstances, the research nurse was available, by telephone, to answer any questions about the study.

If patients wanted to consent to the study at their initial outpatient appointment, this was also permitted.

Randomisation and allocation to intervention

Participants were randomised using a computer-generated randomisation system managed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen. This was available to sites as a web-based or telephone system.

In the eight recruitment sites which offered all three interventions (stratum A), participants were randomly allocated 1 : 1 : 1 to EVLA, foam sclerotherapy or surgery using treatment allocation by minimisation. In the three sites which offered only two of the interventions (stratum B), participants were randomly allocated 1 : 1 to foam sclerotherapy or surgery. Each of these two strata (based on treatment options available at the trial centre) had its own separate treatment allocation application. For each application, the minimisation algorithm included centre, age (< 50 years, ≥ 50 years), sex, presence of GSV or SSV, and unilateral or bilateral veins.

After randomisation, participants were placed on the appropriate waiting list. The aim was to keep participants blinded to their treatment allocation until around 2 weeks prior to their treatment. Around 2 weeks prior to treatment, an appointment for treatment was issued by the hospital; at this time the trial office also informed the participant of his or her randomisation. However, at some sites, local processes meant that participants were informed of their randomisation by site staff in advance of this. The delay in informing participants about their treatment allocation was an attempt to minimise the possibility of unequal dropout between the arms.

A letter was sent to the participant's general practitioner (GP) at trial entry to inform them that their patient had agreed to participate in the trial. Around the time that the participant was informed of his or her treatment allocation, a second letter was sent to the GP informing them of the allocation.

Trial interventions

Surgical treatment

The aim of surgical treatment is to perform saphenofemoral or saphenopopliteal ligation, ligate the groin or popliteal tributaries, remove the incompetent main varicosed truncal vein through inversion stripping and perform phlebectomies for non-truncal varicosities as a combined single procedure. Surgical treatment was performed under a general or regional anaesthetic.

Foam sclerotherapy

The aim of foam sclerotherapy is to fill the incompetent vein with sclerosant under ultrasound guidance by a process of chemical ablation. STS was used as the sclerosant; 3% was used for main truncal veins and 1% for non-truncal varicosities.

The patient was placed in the reverse Trendelenberg position. A needle was inserted into the incompetent GSV or SSV under ultrasound control. The leg was then raised and sclerosant foam [via 2-ml double-syringe Tessari technique, one part (0.5 ml) STS and three parts (1.5 ml) air, with at least 20 passages] injected. Immediately after injection, it was recommended that there was no movement of the patient or leg for 2–5 minutes, no Valsalva manoeuvre and no muscle activation. In line with the European consensus guidelines (published at the time of writing the protocol), a maximum of 12 ml of foam was recommended for use at one sitting.[21]

At the 6-weeks appointment, the need for further foam sclerotherapy to truncal and/or non-truncal veins was assessed. The protocol allowed for a maximum of four treatment sessions of foam sclerotherapy to be offered if this was required to treat all the varicose veins and varicosities.

Sodium tetradecyl sulphate was purchased from routine NHS suppliers by each recruitment site. At the outset of the trial, the STS used was labelled as an investigational medicinal product (IMP) for use in the trial. Part way through the study, a substantial amendment was approved such that routine stocks of STS could be used in the trial and did not require to be labelled as an IMP.

Sodium tetradecyl sulphate was securely stored at room temperature or in a refrigerator in the ward, clinic or theatre. Minimum and maximum temperatures were recorded regularly by the study nurse. Temperature deviations were noted. STS would have been destroyed if the maximum storage temperature had exceeded 40 °C (stability data given in the prescribing information leaflet show that STS is stable for up to 6 months at 40 °C).

Endovenous laser ablation

The aim of EVLA is to destroy the incompetent vein by thermal ablation. EVLA involves cannulating the GSV at the lowest point of incompetence (mid-calf for SSV) under ultrasound guidance. The leg was treated flexed and externally rotated at the hip, with the knee slightly flexed. First a guide wire was inserted and then a 5-Fr catheter passed over this with the tip positioned 0.5–1 cm distal to the junction. The laser fibre was inserted as far as the tip of the catheter. The catheter was then withdrawn 2 cm so that the laser fibre protruded beyond the catheter. The table was then placed in the Trendelenberg position, and cold saline tumescent with lignocaine (Xylocaine®, AstraZeneca) infiltrated along the length of the trunk vein. This provided anaesthesia, compression of the vein around the catheter and absorption of heat. The laser fibre was fired continuously during stepwise or continuous withdrawal, aiming to achieve a target delivery of at least 70 J/cm. EVLA was carried out under local anaesthetic.

The treatment protocol allowed for the immediate treatment of a below-knee incompetent GSV with foam sclerotherapy if laser access was not possible at the site. If required, this was done at the same treatment session to the level of the mid-calf.

In one of the study sites (Hull), the protocol allowed phlebectomies for non-truncal varicosities to be performed at the same time as the EVLA.

At the 6-weeks appointment, the need for foam sclerotherapy to treat any non-truncal varicosities was assessed. The protocol allowed a maximum of four treatment sessions of foam sclerotherapy to be offered, if required, to treat all varicose veins.

Post-procedure compression

After all procedures, post-procedure compression was recommended for 10 days. For foam sclerotherapy, an attempt was made to standardise the type of bandaging and stockings used but this was not possible across all sites owing to local purchasing agreements.

Outcomes

The primary patient-reported outcome was disease-specific QoL (assessed at 6 months using the AVVQ[58]) and generic QoL (assessed at 6 months using the EQ-5D and SF-36 physical and mental component scores).

The AVVQ is an instrument designed to assess the perceived health of patients with varicose veins, and has been shown to be valid, reliable and responsive to change.[9,59,60] It is used as the disease-specific measure in the NHS PROMs.[44,61] The instrument comprises 12 questions and a set of manikin legs, on

which participants are asked to draw their veins. Possible scores range from 0 to 100, though scores close to 100 can only be achieved if there are extensive veins covering the front and back of both legs.

The SF-36 has been validated and shown to be reliable.[61] It is widely used to assess generic QoL across different clinical conditions. The 36 questions in the SF-36 are scored as eight separate domains (vitality, physical functioning, bodily pain, general health, role – physical, role – emotional, social functioning, mental health) and as two summary scores (physical component summary, mental component summary). Though it may be presented as an overall score, we have not chosen to do this in CLASS on account of the lack of sensitivity. All scales are scored from 0 (worst QoL) to 100 (best QoL).

The EQ-5D was developed by the EuroQoL group as a single index valuation for health status. The version used in CLASS is the EQ-5D-3 levels (EQ-5D-3L), which has five questions (or dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with three response options, and a VAS where respondents are asked to rate their current health-related quality of life (HRQoL). Responses to the five questions equate to 243 health states. Scores range from –0.594 to 1.

Secondary outcome measures included:

- costs to the health service and patients and any subsequent care
- clinical success of venous intervention at 6 weeks and 6 months
- anatomical success of venous intervention at 6 weeks and 6 months
- disease-specific and generic QoL (at 6 weeks: AVVQ, SF-36 physical and mental components and domains, EQ-5D and EQ-5D VAS; at 6 months: SF-36 domains and EQ-5D VAS)
- behavioural recovery.

Measurement of secondary outcomes

Costs to the health service and participants and any subsequent care

This is fully described in *Chapter 9*. Projected 5-year costs are described in *Chapter 10*.

Clinical success

This was determined by the VCSS and a VAS at baseline, 6 weeks and 6 months. The VAS consisted of an unmarked line of 10 cm length, which had at the two extremes (1) no varicose veins on the left boundary, and (2) worst possible veins on the right boundary. This was completed by both the patient and the research nurse. It was used to assess the presence of varicose veins at baseline and residual varicose veins at 6 weeks and 6 months. Specific complications, which may affect clinical success, were recorded at the time of treatment and also at 6-weeks and 6-months follow-up.

Anatomical success

The duplex findings in the CLASS study were reported by an independent technician, using a standardised proforma, which recorded the presence of patency/obliteration and reflux (of one greater than 1 second at specific anatomical segments) (*Box 1*). The entire truncal vein was scanned, and if reflux and/or patency was identified at any site, this was recorded as occurring at the nearest site recorded on the proforma.

The joint statement from the Venous Forum and Society of Interventional Radiology (2007)[62] recommended reporting standards for endovenous ablation in the treatment of venous insufficiency. Anatomical success was defined as successful ablation *of the entire treated segment* of the target vein (absent flow or disappearance of the vein on duplex ultrasound). This guidance was used in the CLASS study. We defined complete anatomical success for the GSV as complete occlusion at the groin (within 3 cm of the common femoral vein), complete occlusion at mid-thigh and either an occluded or a patent but non-refluxing GSV above the knee. A partial success was defined as patency at one of the predefined segments of the treated GSV; this was further subclassified as refluxing or non-refluxing. Everything else was defined as a failure.

BOX 1 Specific anatomical segments assessed with duplex scan

Groin – GSV (flush with common femoral vein, i.e. within 1 cm).

Groin – GSV (within 3 cm of common femoral vein).

Common femoral/superficial vein.

Mid-thigh – GSV.

Above knee – GSV.

Below knee – GSV.

SSV (flush with popliteal vein, i.e. within 1 cm).

SSV (within 3 cm of popliteal vein).

Popliteal vein.

Mid-calf – SSV.

For the SSV, a complete success was defined as occlusion within 3 cm of the popliteal vein and complete occlusion at mid-calf. A partial success was defined as patency at one of the predefined segments of the treated GSV; this was further subclassified as refluxing or non-refluxing. Everything else was defined as a failure.

Where a participant had GSV and SSV involvement, a complete success for the whole study leg was achieved when there was a complete success for both GSV and SSV. A failure occurred when there was a failure for both GSV and SSV. If either GSV or SSV was a partial success, or one was a complete success and the other a failure, then it was considered to be a partial success for the whole leg. If there was a partial success for the whole leg and no reflux in either GSV or SSV, then it was classed as a partial success without reflux. Where the participant had GSV or SSV involvement only, then the outcome for the whole study leg was the same as the outcome for the vein.

Disease-specific behavioural recovery

The assessment of behavioural recovery required the development of a specific instrument, and this is discussed in *Chapter 8*. The timing and instruments used for data collection are summarised in *Table 3*; more detail is provided in *Data collection*.

Data collection

Recruitment appointment (baseline, before randomisation)

The disease-specific and generic QoL instruments (AVVQ, EQ-5D and SF-36) and the Illness Perception Questionnaire – Revised (IPQ-R)[63] were combined into a single questionnaire for the participant to complete. Participants were asked to complete this questionnaire at baseline (at the recruitment visit). Participants could opt to complete this at home, and if they did not return this within 3 weeks, they were sent a reminder letter, a further copy of the questionnaire and a reply paid envelope. Early on in the recruitment phase, the randomisation system was amended such that participants could not be randomised until the questionnaire had been completed.

TABLE 3 Timing of instruments

Time point	Completed by participant	Completed by research nurse/ clinician/technician
Baseline (before randomisation)	Questionnaire completed at clinic (or by post) including:	Personal details, GP, best contact, etc.
	AVVQ	Duplex scan
	EQ-5D	Vein involvement
	SF-36	VCSS
	IPQ-R	CEAP classification
		Baseline demographic factors
After randomisation, before treatment	Questionnaire completed by post including:	None; participant not at clinic
	IPQ-R	
At treatment appointment(s)	VAS completed at clinic assessing pain of procedure	Procedural details
		Complications of procedure
6 weeks after treatment	Questionnaire including:	Presence/absence DVT
	AVVQ	Presence/absence residual varicosity
	EQ-5D	Anatomical success
	SF-36	VCSS
	Time to return to work/normal activity	Complications
	Behavioural recovery questionnaire	For patients treated with EVLA or foam, details of further foam injections
	Recollection of pain during treatment and pain during follow-up	
6 months after treatment	Questionnaire including:	Presence/absence DVT
	AVVQ	Presence/absence residual varicosity
	EQ-5D	Anatomical success
	SF-36	Complications
	IPQ-R	VCSS
	Economic questions	

IPQ-R, Illness Perception Questionnaire – Revised.

Participants were asked to rate their varicose veins on a VAS (from 'no varicose veins' to 'the worst varicose veins I can imagine'). Independently, the research nurse also completed an identical VAS.

The baseline clinical form – incorporating CEAP and VCSS for both legs, duplex scan information and vein involvement in relation to the study leg, as well as some demographic information including height, weight, employment status, previous treatment and previous DVT – was also completed at the recruitment appointment.

Personal details, including GP details and a 'best contact', were also collected at recruitment. Participants were asked to nominate a best contact, ideally someone who did not live at the same address as them, who could be contacted if contact with the participant was lost.

After randomisation, before treatment

The pre-treatment questionnaire included the IPQ-R. Approximately 2 weeks before the treatment appointment, the questionnaire was sent to the participant, along with a reply paid envelope. Participants were asked to complete and return this before they attended for treatment. In view of the time frame for completion, reminder letters were not sent for this questionnaire. In some circumstances (e.g. when the treatment date was added retrospectively to the trial database, or immediately before the treatment appointment), it was not appropriate to send the questionnaire as it could not be completed before the treatment appointment.

Treatment appointment

A treatment-specific case report form (CRF) was completed by the treating surgeon (or delegate) after each treatment appointment. The information collected included information specific to the procedure, the grade of surgeon (and, if appropriate, the anaesthetist), how long the procedure took, details of the bandaging, any immediate complications associated with the treatment, whether or not the patient was hospitalised after the treatment and whether or not the contralateral leg was treated contemporaneously. If the participant was undergoing treatment other than the treatment to which he or she had been randomised, the CRF captured this information, together with information about the actual treatment received.

After bandaging, participants were asked to rate the pain experienced during treatment on a VAS ranging from no pain to the worst imaginable pain.

Six-weeks follow-up appointment

Participants were invited to attend for a 6-weeks follow-up appointment. At the appointment, the research nurse carried out a clinical examination of the study leg and completed a CRF incorporating the VCSS and CEAP. The technical success of the treatment was assessed by duplex scanning, performed by an independent, fully trained technician as described above.

Information about any complications or side effects was also recorded. The research nurse and participant assessed the presence of varicose veins using a VAS (ranging from 'no varicose veins' to 'the worst varicose veins I can imagine').

Participants treated with EVLA or foam sclerotherapy were assessed for further foam sclerotherapy treatment. In some cases this was carried out at the 6-weeks appointment; in other cases the participant returned to the clinic at a later date for this.

As at baseline, the disease-specific and generic QoL instruments (AVVQ, EQ-5D, SF-36) were combined into a single questionnaire for completion by the participant. The Behavioural Recovery After treatment for Varicose Veins (BRAVVO) instrument relating to behavioural recovery, including time to return to work/normal activities, was also included in this questionnaire (the development of this instrument is described in *Chapter 8*). Two questions on pain were also included. Participants were asked to rate, on a VAS ranging from no pain to the worst imaginable pain, the worst pain experienced while (1) having the treatment and (2) recovering after treatment.

Participants who opted to take the questionnaire home were provided with a reply paid envelope for its return. Participants who failed to return their questionnaire within 3 weeks were sent a reminder letter, a further copy of the questionnaire and a reply paid envelope. Participants who failed to attend for a follow-up appointment were offered a second appointment. If they failed to attend this, they were sent the questionnaire, covering letter and a reply paid envelope for its return. Again, those who failed to return their questionnaire within 3 weeks were sent a reminder letter, a further copy of the questionnaire and a reply paid envelope.

Six-months follow-up appointment

The 6-months follow-up took a similar form to the 6-weeks follow-up. Participants were invited to attend for a 6-months follow-up appointment. At the appointment, the research nurse carried out a clinical examination of the study leg and completed a CRF incorporating the VCSS and CEAP. The technical success of the treatment was assessed by duplex scanning (as described for the 6-weeks follow-up). Where possible, an individual patient was scanned by the same technician at each time point using the study designated duplex scanner. Information about complications and side effects of treatment was also recorded. The presence of varicose veins was assessed by both the participant and the research nurse using a VAS (as previously described). The research nurse also reviewed the hospital medical records to collect information on any hospital appointments or admissions.

The disease-specific and generic QoL instruments (AVVQ, EQ-5D, SF-36) and the IPQ-R were again combined into a single questionnaire for the participant to complete. Questions relating to resource use (primary and secondary care services), self-purchased health care, and participant time and travel costs were included in the 6-months questionnaire only (for more details see *Chapter 9*). Participants could opt to complete the questionnaire at home; the same reminder schedule was used as for the 6-weeks questionnaire. Participants who failed to attend for the 6-months appointment were offered a second appointment and, if they failed to attend this, a copy of the questionnaire was sent to them, along with a covering letter and a reply paid envelope, with a reminder 3 weeks later.

Data management

A secure, bespoke study database was developed which site staff could access over the internet. Password-protected access was provided such that sites could only view data from their own site. All data collected during the course of the research were kept strictly confidential and accessed only by members of the trial team. Patients' details were stored under the guidelines of the 1988 Data Protection Act.[64] Patients were allocated an individual study number, and this number (rather than the participant's name) was used to identify study paperwork.

Clinical data were entered into the database by the research nurse working in each hospital site, together with data from questionnaires completed at clinic. Data from questionnaires returned by post to the study office were entered by staff based there.

Staff in the study office worked closely with local research nurses to ensure that the data were as complete and accurate as possible. Extensive range and consistency checks further enhanced the quality of the data.

Pharmacovigilance and safety reporting

A serious adverse event (SAE) was defined as any medical occurrence that:

- resulted in death
- was life-threatening (i.e. the subject was at risk of death at the time of the event)
- required inpatient hospitalisation or prolongation of existing hospitalisation
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was an important medical event, which may not have been immediately life-threatening or resulted in death or hospitalisation but may have jeopardised the patient or required intervention to prevent one of the other outcomes listed in the definition.

An adverse reaction was defined as an adverse event judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the medicinal product (i.e. STS).

An unexpected adverse reaction was defined as an adverse reaction, the nature and severity of which were not consistent with the applicable product information. We defined the following SAEs as potentially 'expected':

- DVT (following foam sclerotherapy, EVLA, surgery)
- pulmonary embolism (following foam sclerotherapy, EVLA, 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, EVLA, surgery)
- injury to a motor nerve (femoral, tibial or peroneal nerve) (following surgery)
- transient ischaemic attack (following foam sclerotherapy)
- migraine (following foam sclerotherapy).

All other SAEs were defined as unexpected.

Adverse events during, or immediately following, treatment were collected on the treatment CRF before discharge. In line with current clinical practice, participants were advised to contact their GP if they experienced an adverse event between the period following treatment and the 6-weeks follow-up appointment. At each follow-up visit, participants were asked if they had experienced any adverse events; these were collected on the appropriate follow-up CRF.

All SAEs were recorded as such using the SAE form, and reported to the trial office and to the sponsor within defined time lines. For all SAEs, the local principal investigator was asked to determine whether or not the event was likely to have been caused by study treatment.

Suspected unexpected serious adverse reactions (SUSARs) would have been reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Research Ethics Committee in accordance with prescribed time lines.

Trial oversight

The University of Aberdeen acted as sponsor for the study.

Independent trial steering and data monitoring committees were established. The Trial Steering Committee (TSC) comprised an independent chairperson (a vascular surgeon) and two further independent members (a vascular surgeon and a trials methodologist). The TSC met approximately annually over the course of the trial.

The Data Monitoring Committee (DMC) comprised an independent chairperson (a vascular surgeon) and two further independent members (a trials methodologist and a statistician). The DMC met approximately annually.

Ethics and regulatory approvals

The trial and subsequent amendments were reviewed and given a favourable opinion by Scotland A Research Ethics Committee (reference 08/MRE0024) and local research and development departments. The trial was classed as a clinical trial involving an investigational medicinal product (CTIMP) because of the use of STS in the foam sclerotherapy arm, and was therefore covered by the EU Clinical Trials Directive. Clinical trial authorisation (CTA) was provided from the MHRA (EudraCT 2008-001069-26, CTA 21583/0206/001). The trial was conducted according to the principles of good clinical practice and was registered and assigned an International Standard Randomised Controlled Trial Number (ISRCTN51995477).

Protocol amendments after trial initiation

A number of protocol revisions were made after trial initiation. These included:

- clarification of the techniques for undertaking foam sclerotherapy and EVLA treatment
- providing guidance on the labelling and storage of STS, and subsequently removing the requirement to label STS as an IMP
- assessment of behavioural recovery at 6 weeks rather than 6 months
- inclusion of the assessment of pain
- revision of the 'expected' adverse events in light of new evidence
- addition of an exclusion criterion relating to migraine.

Patient information leaflets were revised in light of new evidence. Adaptations of study administrative processes (for example the use of additional letters, revisions to letters, the use of the clinic log) were also implemented.

Sample size and power

At the outset of the study, we proposed a sample size of 1015 participants from six hospitals across the two strata. We anticipated that four hospital sites would offer three treatment options (surgery, foam sclerotherapy and EVLA; stratum A), and that two hospitals would offer two treatment options (surgery and foam sclerotherapy; stratum B). The proposed sample size is shown in *Table 4*. Based on previous studies,[10,65] we suggested that it would be reasonable to expect differences between surgery and minimally invasive treatment (foam or EVLA) of approximately 0.25 of a standard deviation (SD) on the QoL instruments at 6-months follow-up (in particular, this would equate to a five-point shift in the EQ-5D score). This estimated difference of 0.25 SDs was observed in Short Form questionnaire-6 Dimensions (SF-6D) and EQ-5D scores in the small trial by Ratcliffe *et al.*[10] which compared conventional surgery with sclerotherapy.

TABLE 4 Target recruitment in each of the stratum

Stratum	EVLA	Foam	Surgery
Stratum A (four hospitals)	245	245	245
Stratum B (two hospitals)	–	140	140
Total	245	385	385

Foam versus surgery

For this primary comparison, strata A and B can be combined without introducing any bias. A trial with 385 patients in each group (total 770 patients) will have at least 90% power at a 5% significance level to detect a change of 0.25 SDs in both AVVQ and EQ-5D. Adjusting for baseline score allows the sample size to be decreased by a factor of 1 – correlation squared, so including 385 participants allows for a 10% loss to follow-up at 6 months (assuming a correlation between baseline and 6-months scores of at least 0.31). A correlation of 0.31 is, in our experience, conservative for QoL studies, but should the loss to follow-up be 15%, the study would still have 90% power to detect a difference of 0.25 SDs. Cost savings will be sensitive to the number of participants with recurrent varicose veins requiring reintervention 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).

Endovenous laser ablation versus surgery

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 SDs. Given adjustment for baseline measures, this allows for a 10% loss to follow-up.

Recruitment to the trial was lower than anticipated for a number of reasons. These included a lower-than-anticipated proportion of varicose vein referrals who met the eligibility criteria, 'rationing' of varicose vein treatment at some sites leading to a sharp decline in the number of patients being referred for treatment, and a lower-than-anticipated proportion of eligible patients agreeing to take part. Additional recruitment sites were sought in an attempt to compensate for the recruitment shortfall, but few UK sites offered the appropriate treatment options to enable them to participate in the study. Despite some additional sites, and an extension to the recruitment period, the original recruitment targets were not met. Thus, the DMC and TSC were asked to consider a revised recruitment target of 779 (*Table 5*).

We provided the following justification for this request. The correlation, pooled across trial arms, between the AVVQ at baseline and 6 months post surgery was 0.39, and this has the effect of providing greater power than originally assumed. In the surgery versus foam comparison, the power achieved with the sample size of 283 in each arm would be equivalent to 334 in each arm if no correlation was observed. Similarly, the power achieved with the sample size of 211 in each arm of the surgery versus EVLA comparison would be equivalent to 249 in each arm if no correlation was observed.

However, at 6 months the response to follow-up was 89%, 1% of questionnaires did not include sufficient data to derive a valid AVVQ and the proportion of participants withdrawn (including those withdrawn prior to receiving an intervention) was 7%. Together, these factors indicated that a valid AVVQ could be expected in 82% of the planned sample.

Therefore, the sample size was effectively 275 (i.e. 82% of 334 in each arm of the surgery vs. foam comparison) for the purpose of determining power (*Table 6*).

Similarly, the sample size was effectively 205 in each arm of the surgery versus EVLA comparison (*Table 7*).

Note that although the proposed revised trial sample size was decreased, there was no change to the target differences assumed to be clinically important (0.25 SDs); the only amendment to the sample size calculation was a decrease in the power of the study to detect a 0.25-SD change. Both the DMC and TSC agreed this amendment.

TABLE 5 Proposed revised sample size in each stratum

Stratum	Total	EVLA	Foam sclerotherapy	Surgery
Stratum A	635	211	211	211
Stratum B	144	–	72	72
Total	779	211	283	283

TABLE 6 Power calculation for foam vs. surgery comparison

Target	Effective sample size in each arm	Detectable effect size with 90% power (SDs)	Power to detect 0.25 SDs (%)
Previous	350	0.25	91
Revised	275	0.28	83

TABLE 7 Power calculation for EVLA vs. surgery comparison

Target	Effective sample size in each arm	Detectable effect size with 80% power (SDs)	Power to detect 0.25 SDs (%)
Previous	258	0.25	81
Revised	205	0.28	72

Statistical analysis

The trial analysis was by intention to treat (all participants remained in their allocated group for analysis), giving the least biased estimate of effectiveness between interventions. Three comparisons were considered for the main trial analysis: (1) surgery versus foam sclerotherapy, (2) surgery versus EVLA and (3) EVLA versus foam sclerotherapy. Participants from all centres were included in the analysis of comparison (1), and participants from only those centres randomising to all three treatments were included in the analysis of comparisons (2) and (3). A single principal analysis of the randomised trial was planned when all participants had been followed up for 6 months after treatment. Study analyses were conducted according to a statistical analysis plan, using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

The primary outcome measures (AVVQ, EQ-5D and SF-36 scores at 6 months) and all secondary outcome measures (AVVQ, EQ-5D and SF-36 scores at 6 weeks; VCSS, presence of residual varicosities, truncal vein ablation and complication rates at 6 weeks and 6 months; pain at time of treatment and at 6 weeks) were presented as summaries of descriptive statistics at each time point and comparisons between groups were analysed using generalised linear models (GLMs). All analyses were adjusted for minimisation covariates (sex, age group, saphenous involvement, disease laterality and centre) and, where appropriate, for baseline scores (for AVVQ, EQ-5D, SF-36 and VCSS). If there was a discrepancy between the minimisation covariate used in the randomisation process and the data recorded in the baseline clinical form, then the latter was used in the reporting of descriptive statistics and for adjustment in the analyses. No adjustment was made for multiple comparisons. However, for the secondary outcome measures, we considered differences to be significant only for p-values < 0.005. The models used to analyse the continuous outcomes were repeated measures mixed models with a compound symmetry covariance matrix and centre fitted as a random effect. Truncal vein ablation rates were analysed using ordinal logistic regression and complication rates were analysed using binary logistic regression. Estimates of treatment

effect size were expressed as the fixed effect solutions in the mixed models and odds ratios (ORs) in the logistic regression models. For all estimates, 95% confidence intervals (CIs) were calculated and reported.

Sensitivity analyses were carried out on the primary outcome to investigate the impact of missing data under various assumptions following recently published recommendations.[66] Complete follow-up data were used in the sensitivity analyses, with values imputed for any missing AVVQ score at 6 months. The repeated measures models used in the primary analysis assumed data to be missing at random,[67] whereas the sensitivity analyses used multiple imputation where data were assumed to be missing not at random, because we considered scenarios where there might be systematic differences between missing and observed values and also where this differed between groups. The first sensitivity analysis assumed no systematic difference and imputed values were obtained from the generation of 10 data sets and based purely on observed values (minimisation covariates and AVVQ scores at baseline and 6 weeks). The remaining sensitivity analyses adjusted the imputed values in the initial sensitivity analysis by either adding two points to the imputed AVVQ scores or subtracting two points. These adjustments were then repeated in one arm only, and repeated again by applying the adjustments in the other arm only. We considered two points on the AVVQ score to be more than the minimum clinically important difference, and hence a meaningful systematic difference to test in the sensitivity analyses.

The Aberdeen Varicose Vein Questionnaire

The AVVQ consists of 19 items (a diagram at the beginning on which respondents mark the location and extent of their varicose veins, followed by 12 ordinal response items, of which six require separate responses for each leg). The outcome measure is scored from 0 to 100 (higher values indicate worse QoL), and scores were calculated using weightings for each response in the questionnaire. Where a response was omitted by the respondent, the score for that item was removed from the denominator so that participants could still score between 0 and 100 even if the questionnaire was not fully completed.[59] If the participant had unilateral disease at the time of completing the questionnaire (determined from the veins drawn on the diagram), then, for unanswered questions which related to the healthy leg only, it was assumed that the response should be 'no' or 'none at all' and a value of 1 was imputed. Once this was executed, any questionnaires with more missing responses than non-missing responses (i.e. 10 missing items or more) were considered not to have valid scores.

The Venous Clinical Severity Score

The VCSS consists of 10 ordinal response items, each with four levels (coded from 0 to 3). The overall score was calculated as the sum of the values across each of the 10 responses, so that a VCSS score could potentially be in the range from 0 to 30 (higher scores indicate greater severity). If the response to question 7 was 'no active ulcers' and the responses to questions 8 and 9 (relating to active ulcers) were missing, then questions 8 and 9 were assigned a value of zero. For other missing items, if the equivalent response was available from the AVVQ then these missing responses were assigned the appropriate value. A valid VCSS was not obtainable for participants for whom there remained any missing responses.

Process evaluation

Background

As it was not possible for participants to be blinded to their treatment, several steps were taken to increase our confidence in the trial results based on the primary QoL outcomes. As much as possible, information provided to participants at recruitment, after randomisation and following treatment was standardised.

We also conducted a theory-based process evaluation to identify possible confounding variables, for example, expectations or concerns that might differ between treatment groups after participants were informed of the treatment they would receive and that might, in turn, influence recovery behaviours or QoL. The theoretical basis for this process evaluation was the common-sense self-regulation model (CS-SRM).[68]

The CS-SRM proposes that people respond to a potential health threat in terms of their perceptions, beliefs and expectations ('cognitive' representations) and also in terms of anxieties and concerns ('emotional' representations). People use a range of coping behaviours (e.g. self-medicating, seeking social support or perhaps avoidance) to manage and regulate these representations. Systematic review evidence suggests that illness representations play a significant role in help-seeking behaviour and adherence to treatment recommendations.[69,70]

Questionnaire measures have been developed and validated to assess the proposed domains of illness representations. The domains are illness identity; causes; timeline; consequences; control; coherence; and emotion. *Table 8* presents the label, a brief explanation and an example questionnaire item for each of the domains of the illness perceptions framework.

Methods

The most frequently used, validated scale to assess illness representations is the IPQ-R.[63] The IPQ-R assesses each of the domains in the illness perceptions framework. This questionnaire was administered to trial participants at baseline, following randomisation and 6 months after treatment.

We were particularly interested in whether or not participants in any of the trial arms reported different illness perceptions after they were notified of the treatment to which they had been randomised (but before treatment). We were also interested in whether or not illness perceptions improved following treatment, particularly with regard to the domain of treatment control, as this would likely reflect participants' perceptions of the effectiveness of their treatment, and timeline and consequences, as these would likely reflect the extent to which participants' expectations were exceeded following treatment.

TABLE 8 The illness perceptions framework as proposed in the CS-SRM and as measured in the IPQ-R[63]

Domain label	Explanation	Example questionnaire item
Identity	What is the condition and its experienced symptoms?	Symptom checklist (see *Identity domain*)
Cause	What are the causes of the condition?	Cause checklist (see *Identity domain*)
Timeline (acute/chronic)	How long will the condition last?	My varicose veins will last a long time
Timeline (cyclical)	Is the condition experienced as episodes?	My symptoms come and go in cycles
Consequences	How serious are the consequences of the condition for the person's everyday life?	My varicose veins have major consequences on my life
Personal control	To what extent does the person have control over managing or curing the condition?	Nothing I can do will affect my varicose veins (reverse code)
Treatment control	To what extent is treatment effective in managing or curing the condition?	My treatment will be effective in curing my varicose veins
Illness coherence	To what extent does the person understand the condition and the way the treatment is proposed to work?	My varicose veins are a mystery to me
Emotional representations	How worried is the person about having the condition?	When I think about my varicose veins I get upset

Analysis

Identity domain

In the IPQ-R, participants are presented with a number of symptoms, some that might be expected to occur as a result of varicose veins, and some unrelated to varicose veins. Participants are asked to identify symptoms that they have experienced since developing varicose veins, and whether or not they believe that these symptoms are related to their varicose veins. The IPQ-R was scored according to the method outlined on the Illness Perception Questionnaire (IPQ) website (www.uib.no/ipq). The 'illness identity score' is the number of symptoms that are both experienced by the participant and correctly identified as being related to their varicose veins.[63] The symptoms are pain, hardening of the skin, redness of the skin, swelling of the ankle, discolouration or brown staining on the leg, and breaks in the skin or ulcers on the leg. The questionnaire also lists unrelated symptoms (sleep difficulties, stiff joints, weight loss, dizziness, fatigue, sore eyes, breathlessness, loss of strength), but these questions do not count either positively or negatively towards the individual's overall illness identity score. Possible identity scores range between 0 and 6.

The 'percentage of symptoms correctly identified as being related to varicose veins' is another way of representing illness identity,[63] but differs from the identity score in that it only takes account of the subset of the six symptoms that the participants reported having experienced. These are calculated as a percentage for each participant. Where fewer than six symptoms are experienced, these percentages are higher than the corresponding identity score expressed as a proportion out of six.

Other domains

The other measures of illness perception are presented as mean scores out of 30 [for timeline (acute/chronic), consequences, personal control and emotional representations], 25 (for treatment control and illness coherence) or 20 [for timeline (cyclical)], with higher scores indicative of greater illness representation.

The results of the process evaluation for the comparison of foam sclerotherapy and surgery are presented in *Chapter 5* and those for the comparison of EVLA, foam sclerotherapy and surgery in *Chapter 6*. Discussion of the process evaluation is given in *Chapter 7*.

Chapter 4 Baseline characteristics

This chapter provides a brief overview of all patients involved in the study and describes baseline characteristics of the whole cohort of participants pooled across treatment groups. Baseline data broken down by randomised groups are presented in *Chapters 5* and *6*.

Figure 2 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram for the entire CLASS study. In total, 6592 patients with varicose veins were screened for eligibility over 48 months between November 2008 and October 2012. The mean age of those screened was 51 (SD 15) years, and 64% were female. Fifty-one per cent of those screened (3369 patients) met the eligibility criteria and 43% (2847 patients) were ineligible. The eligibility status was unknown (or not recorded in the study clinic log book) for the other 6%. Common reasons for exclusion were recurrent varicose veins, no reflux or reflux < 1 second, veins < 3 mm or > 15 mm in diameter and the presence of comorbidities. Of the 3369 eligible patients, 798 (24%) consented to participate in the trial and 2571 (76%) declined. The most frequent reason for declining to take part was a preference for one form of treatment, and therefore a wish not to undergo randomisation. The reasons for ineligibility and declining to take part are shown in *Table 9*.

Thirteen patients (1.6%) were found to be ineligible after randomisation, including five patients with veins > 15 mm in diameter and three who were later discovered to have recurrent varicose veins. The remainder were ineligible because of patient comorbidities or lack of reflux. These patients were treated as post-randomisation exclusions, and therefore 785 participants were included in the formal trial population.[71]

Eleven participating centres contributed to recruitment, each in one of two strata. The eight centres in stratum A randomised to all three treatment arms, and the three in stratum B randomised to foam sclerotherapy or surgery only, because they were unable to offer EVLA treatment. The numbers of randomised participants recruited, by centre, are shown in *Table 10*.

Recruitment and randomisation took place over a period of 48 months. *Figure 3* shows the recruitment rate over time.

All 785 participants attended for baseline clinical assessment and 779 (99%) completed baseline questionnaires. At the time of primary treatment, 720 (92%) received their randomised allocation, 27 (3%) received a study treatment other than their randomised treatment and 38 (5%) did not receive any of the study treatments.

With regard to those patients who did not receive the treatment to which they were randomised, 10 were randomised to foam sclerotherapy but received EVLA (six patients) or surgery (four patients) as their primary treatment. Reasons given for this included unsuitability for foam (veins considered too wide, history of migraine, dizziness/double vision prior to treatment, needle phobia), patient preference and logistic reasons. Eleven patients were randomised to foam and did not have any treatment within the trial. The most common reason for this was patient preference; two patients failed to attend for treatment/pre-treatment review, and one participant suffered a major stroke prior to treatment and was excluded from treatment and follow-up at this point.

Two patients who were randomised to EVLA received surgery as their primary treatment. In one case, this was because the patient wished to have treatment under general anaesthetic; in the other case, the responsible consultant recommended surgery because of the extensive nature of the veins.

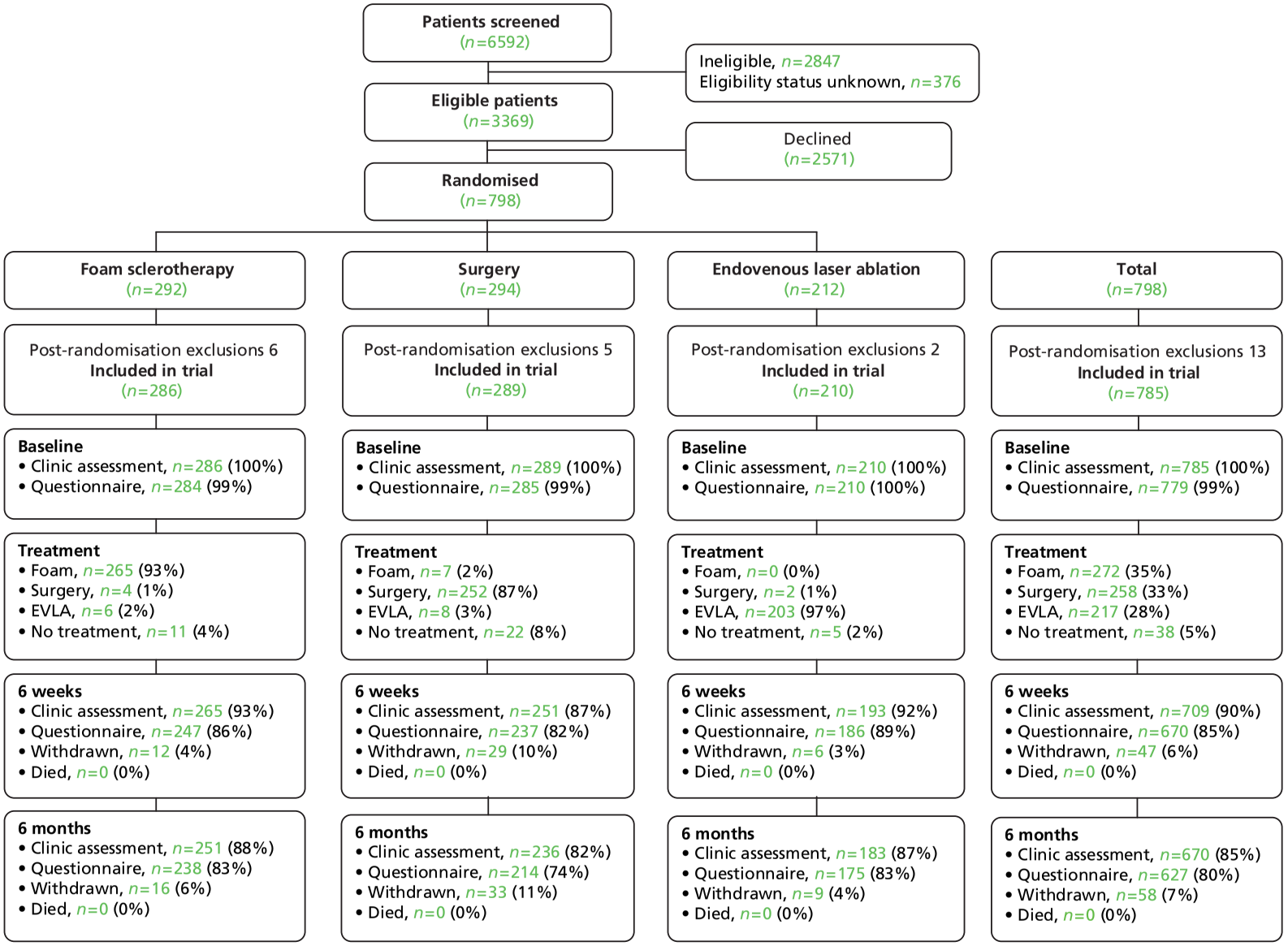

FIGURE 2 Consolidated Standards of Reporting Trials diagram.

TABLE 9 Description of ineligible patients, and the reasons eligible patients declined to take part

Non-randomised screened patients	*n*	%
Reason for ineligibility	2847	
Recurrence	789	27.7
No reflux or reflux < 1 second	624	21.9
Patient comorbidity	384	13.5
GSV or SSV < 3 mm in diameter or > 15 mm	264	9.3
Tortuous veins that are considered to be unsuitable for EVLA	242	8.5
Vein related – no further information	179	6.3
Asymptomatic CEAP grade 2	156	5.5
Thrombosis (current deep-vein incompetence, acute superficial vein thrombosis)	58	2.0
Other	151	5.3
Reason for declining to take part	2571	
Patient preference for surgery	838	32.6
Patient preference for EVLA	761	29.6
Patient preference for foam sclerotherapy	341	13.3
Patient did not want foam sclerotherapy	35	1.4
Patient did not want surgery	17	0.7
Patient did not want EVLA	1	< 0.1
Other reason[a]	554	21.5
Surgeon preference	24	0.9

a This includes patients who declined to give a reason.

TABLE 10 Included participants, by centre and randomised allocation

Stratum	Centre	Foam	Surgery	EVLA	Total randomised	Percentage of total recruitment
A	Aberdeen	72	74	74	220	28.0
	Hull	55	56	54	165	21.0
	Leeds	35	36	35	106	13.5
	Bournemouth	22	24	24	70	8.9
	Newcastle	11	14	13	38	4.8
	Sheffield	5	4	6	15	1.9
	Worcester	4	3	2	9	1.1
	Blackburn	3	2	2	7	0.9
	Stratum A total	**207**	**213**	**210**	**630**	**80.3**
B	Gloucestershire	37	35	N/A	72	9.2
	Exeter	35	34	N/A	69	8.8
	Sherwood Forest	7	7	N/A	14	1.8
	Stratum B total	**79**	**76**	**N/A**	**155**	**19.7**
Total recruitment		**286**	**289**	**210**	**785**	

N/A, not applicable.

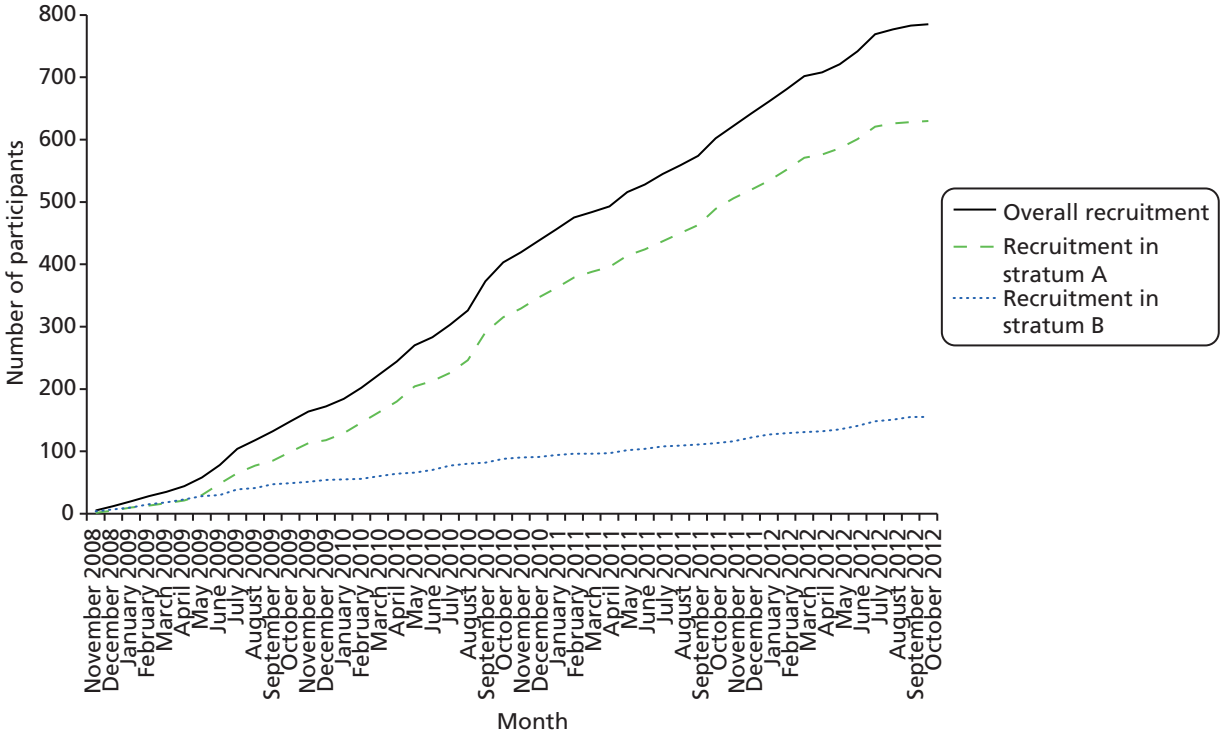

FIGURE 3 Recruitment over time.

Five patients randomised to EVLA did not undergo treatment. Two patients failed to attend for treatment, two declined treatment and one patient had cardiac problems which led to cancellation of planned treatment. Seven participants were randomised to surgery but received foam sclerotherapy as their primary treatment. For two of these, the reason was medical (unfit for general anaesthetic and back problems/concerns regarding anaesthetic/positioning). For the other five, the reasons related to a preference for foam sclerotherapy. Eight participants randomised to surgery opted to have EVLA treatment. All but one of these patients expressed a preference for EVLA after randomisation. One patient attended for surgery but panicked and was then listed for EVLA. Twenty-two patients were randomised to surgery and did not receive any treatment. The majority of these patients indicated a preference not to undergo surgery, but one declined because she was undergoing tests for possible cancer and three moved out of the study area before surgery was carried out.

At 6 weeks after treatment, 709 (90%) attended clinic for follow-up examination and 670 (85%) completed questionnaires. At 6 months, 670 (85%) attended clinic for follow-up examination and 627 (80%) completed questionnaires.

Baseline characteristics of the study participants

The mean age of participants was 49.2 (SD 13.7) years and 57% were female, so the trial cohort was slightly younger and had fewer females than the overall group of patients with varicose veins who were initially screened (*Table 11*). The mean body mass index (BMI) was 27.3 kg/m^2 (SD 4.6 kg/m^2), 61% were in employment and 221 participants (28%) had varicose veins in both legs; these participants nominated their worst leg as their 'study leg'. Eleven per cent of participants had undergone previous varicose vein treatment of their non-study leg and 1% had received previous sclerotherapy for varicose veins in their study leg.

Quality of life

A valid AVVQ score (our primary outcome) was obtained for all but one of the participants who completed a baseline questionnaire, and the mean score was 17.9 (SD 9.5) (*Table 12*). The mean EQ-5D was 0.79 (SD 0.18).

TABLE 11 Baseline characteristics of all study participants

Characteristics	All participants		
Randomised (*n*)	785		
Age (years) (*n*, mean, range)	785	49.2	18–85
Female (*N*, *n*, %)	785	445	56.7
BMI (kg/m^2) (*n*, mean, range)	725	27.3	17–44
Employment status			
Self-employed (*N*, *n*, %)	773	87	11.3
Employed (*N*, *n*, %)	773	468	60.5
Other (*N*, *n*, %)	773	218	28.2
Laterality			
Unilateral (*N*, *n*, %)	785	564	71.8
Bilateral (*N*, *n*, %)	785	221	28.2
Previous history of DVT (*N*, *n*, %)	776	19	2.4
Previous treatment to contralateral leg (*N*, *n*, %)	779	85	10.9
Foam sclerotherapy (*N*, *n*, %)	779	16	2.1
Surgery (*N*, *n*, %)	779	61	7.8
EVLA treatment (*N*, *n*, %)	779	7	0.9
Previous sclerotherapy to tributaries of study leg (*N*, *n*, %)	779	7	0.9

TABLE 12 Quality of life at baseline

QoL measure	All participants		
Randomised (*n*)	785		
AVVQ score (*n*, mean, SD)	778	17.9	9.5
EQ-5D score (*n*, mean, SD)	764	0.79	0.18
VAS (*n*, mean, SD)	771	80.5	15.8
SF-36 summary scores			
Physical component summary score (*n*, mean, SD)	723	48.6	8.3
Mental component summary score (*n*, mean, SD)	723	51.8	9.2
SF-36 domain scores			
Physical functioning (*n*, mean, SD)	738	50.1	8.5
Role physical (*n*, mean, SD)	772	50.0	9.1
Bodily pain (*n*, mean, SD)	772	47.3	8.9
General health (*n*, mean, SD)	772	49.5	8.4
Vitality (*n*, mean, SD)	776	51.3	9.4
Social functioning (*n*, mean, SD)	773	50.7	9.0
Role emotional (*n*, mean, SD)	770	51.0	8.8
Mental health (*n*, mean, SD)	774	51.6	9.4

For SF-36, the mean physical component score of 48.6 (SD 8.3) was lower than the mean mental component score of 51.8 (SD 9.2) and the population norm score for the physical component of 50 (SD 10). This indicates that, compared with the wider population, the study cohort had slightly poorer physical health at baseline and the low SDs suggest that the cohort was a relatively uniform group in terms of QoL. The main factor contributing to the lower physical component score was the bodily pain domain, with a subscale score of 47.3 (SD 8.9).

Physical activity

A summary of physical activity data collected at the baseline clinic assessment is presented in *Table 13*. Thirteen per cent of participants spent most of their time at work sitting (e.g. in an office) and 31% spent most of their time at work standing or walking without requiring much intense physical effort. Twenty-four per cent worked in jobs involving definite physical effort, including handling heavy objects and using tools, and 6% had employment involving vigorous physical activity including handling very heavy objects.

In the week prior to recruitment, 45% of participants engaged in physical exercise such as swimming, jogging, aerobics, football, tennis and gym workouts (including 21% who had exercised for more than 3 hours).

Baseline characteristics of study leg

The majority of participants (653/785, 83%) had GSV reflux only, 56 (7%) had SSV reflux only and the remaining 76 (10%) had both GSV and SSV involvement (*Table 14*). The proportions of participants with left or right leg involvement were similar. The mean widest diameter below the SFJ was 8.7 mm for those with GSV involvement only, and for those with SSV involvement only, the mean widest diameter below the saphenopopliteal junction was 7.5 mm. Of those with any GSV involvement, 90% had reflux above the

TABLE 13 Physical activity at baseline

Physical activity	All participants		
Randomised (*n*)	785		
Physical activity at work			
Mostly sitting (*N*, *n*, %)	761	101	13.3
Mostly standing or walking (*N*, *n*, %)	761	239	31.4
Definite physical effort (*N*, *n*, %)	761	180	23.7
Vigorous physical effort (*N*, *n*, %)	761	44	5.8
Not in employment (*N*, *n*, %)	761	197	25.9
Physical activity in previous week			
Physical activities (*N*, *n*, %)	770	348	45.2
Cycling (*N*, *n*, %)	755	126	16.7
Walking (*N*, *n*, %)	769	756	98.3
Housework/childcare (*N*, *n*, %)	767	674	87.9
Gardening (*N*, *n*, %)	765	473	61.8
Usual walking pace			
Slow (*N*, *n*, %)	771	48	6.2
Steady/average (*N*, *n*, %)	771	374	48.5
Brisk (*N*, *n*, %)	771	293	38.0
Fast (*N*, *n*, %)	771	56	7.3

TABLE 14 Baseline characteristics of study leg

Study leg vein characteristics	All participants		
Randomised (*n*)	785		
Study leg			
Right (*N*, *n*, %)	785	382	48.7
Left (*N*, *n*, %)	785	403	51.3
Saphenous involvement			
GSV only (*N*, *n*, %)	785	653	83.2
Widest diameter (mm) (*n*, mean, range)	587	8.7	3–15
Reflux above knee only (*N*, *n*, %)	520	500	96.2
Reflux above and below knee (*N*, *n*, %)	520	20	3.8
SSV only (*N*, *n*, %)	785	56	7.1
Widest diameter (mm) (*n*, mean, range)	50	7.5	3–15
GSV and SSV (*N*, *n*, %)	785	76	9.7
Widest diameter GSV (mm) (*n*, mean, range)	72	7.2	3–15
Widest diameter SSV (mm) (*n*, mean, range)	66	5.4	3–15
Reflux above knee only (*N*, *n*, %)	60	27	45.0
Reflux above and below knee (*N*, *n*, %)	60	33	55.0
Deep-vein reflux (*N*, *n*, %)	767	100	13.0
CEAP classification			
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	782	0	0.0
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	782	0	0.0
C2 Varicose veins > 3 mm (*N*, *n*, %)	782	429	54.9
C3 Oedema (*N*, *n*, %)	782	102	13.0
C4 Skin and subcutaneous changes (*N*, *n*, %)	782	79	10.1
C4a Pigmentation or eczema (*N*, *n*, %)	782	130	16.6
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	782	11	1.4
C5 Healed venous ulcer (*N*, *n*, %)	782	20	2.6
C6 Active venous ulcer (*N*, *n*, %)	782	11	1.4
VCSS (*n*, mean, SD)	778	5.0	2.5
Presence of varicose veins			
Assessed by participant (*N*, *n*, %)	785	783	99.7
VAS (*n*, mean, SD)	785	5.5	2.2
Assessed by research nurse (*N*, *n*, %)	785	784	99.9
VAS (*n*, mean, SD)	785	3.8	2.2

knee only. All participants had a CEAP classification of C2 or above (reflecting the inclusion criteria for the trial), and 55% had grade C2 veins. The mean VCSS at baseline was 5.0 (SD 2.5). The severity of varicose veins, assessed on a VAS from 0 (none) to 10 (worst possible), recorded higher scores (i.e. a perception of more varicose veins) when assessed by the participant (mean score 5.5, SD 2.2) than when assessed by the research nurse (mean score 3.8, SD 2.2).

Contralateral leg

The baseline CEAP classification and VCSSs are summarised in *Table 15* for the 28% of participants with bilateral disease. The majority of these participants (63%) had a C2 CEAP classification for their contralateral leg; the distribution of CEAP classifications was similar for study legs and contralateral legs. The mean VCSS for contralateral legs was 3.8 (SD 2.3), which was lower than the mean score of 5.0 for the study legs.

Results from the foam sclerotherapy versus surgery comparison, which included patients from all centres ($n = 575$), are described in *Chapter 5*. Results from the foam versus EVLA and EVLA versus surgery comparisons, which included patients in the centres which participated in the three arms ($n = 630$), are described in *Chapter 6*.

TABLE 15 Baseline characteristics of contralateral leg

Non-study leg vein characteristics	All participants		
Randomised (*n*)	785		
Participants with bilateral disease (*N*, *n*, %)	785	221	28.2
CEAP classification			
C2 Varicose veins > 3 mm (*N*, *n*, %)	213	135	63.4
C3 Oedema (*N*, *n*, %)	213	31	14.6
C4 Skin and subcutaneous changes (*N*, *n*, %)	213	16	7.5
C4a Pigmentation or eczema (*N*, *n*, %)	213	27	12.7
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	213	1	0.5
C5 Healed venous ulcer (*N*, *n*, %)	213	2	0.9
C6 Active venous ulcer (*N*, *n*, %)	213	1	0.5
VCSS (*n*, mean, SD)	209	3.8	2.3

Chapter 5 Comparison of surgery and foam sclerotherapy

In this chapter we report the results for surgery compared with foam sclerotherapy, using data from all centres. A discussion of these results is included in *Chapter 7*.

Participants

Five hundred and eighty-six participants were randomised to either foam sclerotherapy or surgery; of these, 11 (2%) were post-randomisation exclusions (see *Chapter 4*), leaving a total of 575 participants included in the trial analysis (286 in the foam arm and 289 in the surgery arm). The CONSORT diagram (see *Figure 2*) describes the flow of participants in the trial.

The proportion receiving treatment as allocated appeared to be higher for foam sclerotherapy (93%) than for surgery (87%). Retention appeared to be slightly higher for foam, in terms of both follow-up clinic assessments and completion of participant questionnaires. The 6-weeks clinic was attended by 93% of participants randomised to foam sclerotherapy compared with 87% of those receiving surgery, and at 6 months the attendance rates were 88% and 82% respectively. The 6-weeks questionnaire was completed by 86% of participants randomised to foam sclerotherapy compared with 82% of those randomised to surgery, and at 6 months the response rates were 83% and 74% respectively. A slightly larger proportion of participants appeared to have withdrawn in the surgery arm at 6 months (11%) than in the foam arm (6%).

Baseline characteristics

Demographic details

The main baseline characteristics of study participants are shown in *Table 16*. There was a good balance between groups for most factors, particularly for age and sex, which were minimisation variables. There was a slight imbalance between groups in terms of bilateral disease. The data shown in *Table 16* were used in the analysis when adjusting for minimisation factors.

Quality of life

Quality of life was assessed prior to the patient being randomised. QoL appeared to be slightly better in the foam group and this is reflected in the AVVQ, EQ-5D and each of the SF-36 components and subdomain scores (*Table 17*). For foam, the baseline AVVQ score was 17.6 (SD 10.0) and for surgery it was 18.2 (SD 9.2) (higher scores indicate worse QoL).

Physical activity

There was a good balance between the groups in terms of physical activity at baseline (*Table 18*).

TABLE 16 Baseline characteristics of study participants: comparison of surgery against foam sclerotherapy

Participant characteristics	Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	286			289		
Age (years) (*n*, mean, range)	286	49.0	19–78	289	49.2	22–85
Female (*N*, *n*, %)	286	162	56.6	289	163	56.4
BMI (kg/m^2) (*n*, mean, range)	269	27.1	17–44	261	27.7	17–44
Employment status						
Self-employed (*N*, *n*, %)	285	37	13.0	282	29	10.3
Employed (*N*, *n*, %)	285	169	59.3	282	179	63.5
Other (*N*, *n*, %)	285	79	27.7	282	74	26.2
Laterality						
Unilateral (*N*, *n*, %)	286	215	75.2	289	196	67.8
Bilateral (*N*, *n*, %)	286	71	24.8	289	93	32.2
Previous history of DVT (*N*, *n*, %)	284	4	1.4	286	9	3.1
Previous treatment to contralateral leg (*N*, *n*, %)	284	30	10.6	287	28	9.8
Foam sclerotherapy (*N*, *n*, %)	284	10	3.5	287	2	0.7
Surgery (*N*, *n*, %)	284	20	7.0	287	22	7.7
Laser treatment (*N*, *n*, %)	284	0	0.0	287	4	1.4
Previous sclerotherapy to tributaries of study leg (*N*, *n*, %)	284	0	0.0	287	4	1.4

TABLE 17 Quality of life at baseline: comparison of surgery against foam sclerotherapy

QoL measure	Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	286			289		
AVVQ score (*n*, mean, SD)	284	17.6	10.0	284	18.2	9.2
EQ-5D score (*n*, mean, SD)	279	0.80	0.18	279	0.78	0.18
VAS (*n*, mean, SD)	282	80.8	15.6	283	80.2	15.6
SF-36 summary scores						
Physical component summary score (*n*, mean, SD)	275	48.9	8.2	275	48.2	8.8
Mental component summary score (*n*, mean, SD)	275	52.4	8.9	275	51.2	9.6
SF-36 domain scores						
Physical functioning (*n*, mean, SD)	283	50.1	8.8	281	50.1	8.3
Role physical (*n*, mean, SD)	284	50.7	8.7	280	49.1	10.0
Bodily pain (*n*, mean, SD)	283	48.2	8.8	282	46.3	9.3
General health (*n*, mean, SD)	279	49.8	8.0	284	49.2	8.9
Vitality (*n*, mean, SD)	283	51.6	9.5	283	50.8	9.5
Social functioning (*n*, mean, SD)	283	51.5	8.1	283	49.8	9.9
Role emotional (*n*, mean, SD)	283	51.3	8.2	279	50.5	9.6
Mental health (*n*, mean, SD)	283	52.1	9.2	282	50.9	9.8

TABLE 18 Physical activity at baseline: comparison of surgery against foam sclerotherapy

Physical activity	Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	286			289		
Physical activity at work						
Mostly sitting (*N*, *n*, %)	280	38	13.6	279	36	12.9
Mostly standing or walking (*N*, *n*, %)	280	102	36.4	279	90	32.3
Definite physical effort (*N*, *n*, %)	280	56	20.0	279	72	25.8
Vigorous physical effort (*N*, *n*, %)	280	15	5.4	279	13	4.7
Not in employment (*N*, *n*, %)	280	69	24.6	279	68	24.4
Physical activity in previous week						
Physical activities (*N*, *n*, %)	284	129	45.4	282	124	44.0
Cycling (*N*, *n*, %)	280	39	13.9	278	55	19.8
Walking (*N*, *n*, %)	285	279	97.9	280	275	98.2
Housework/childcare (*N*, *n*, %)	284	254	89.4	280	243	86.8
Gardening (*N*, *n*, %)	283	187	66.1	279	172	61.6
Usual walking pace						
Slow (*N*, *n*, %)	283	13	4.6	283	18	6.4
Steady/average (*N*, *n*, %)	283	129	45.6	283	144	50.9
Brisk (*N*, *n*, %)	283	121	42.8	283	100	35.3
Fast (*N*, *n*, %)	283	20	7.1	283	21	7.4

Varicose vein characteristics

Baseline characteristics describing the varicose veins in the participants' study and contralateral legs are shown in *Tables 19* and *20* respectively. The groups are well balanced across the majority of factors (except for deep-vein reflux, where 17% in the foam group were affected compared with 9% in the surgery group).

Treatment received

Table 21 summarises the primary interventions received (i.e. excluding any delayed secondary foam treatments), summarised by randomised allocation. For participants randomised to foam, 96% of those who received treatment had their treatment as randomised (i.e. had foam sclerotherapy). The equivalent proportion in the surgery arm was 94%. The participants who did not undergo their randomised treatment are described in *Chapter 4*.

Procedure and treatment time

At the time of the primary intervention, more participants in the surgery arm had treatment to non-truncal varicosities (90%) than in the foam arm (31%) (see *Table 21*). More patients in the surgery arm (15%) had their contralateral leg treated at the same time than in the foam arm (3%).

The mean treatment duration (the time taken from preparation of the patient to completion of bandaging) was longer for surgery (53 minutes, SD 22.9 minutes) than for foam (19 minutes, SD 10.6 minutes). Foam sclerotherapy was performed by consultants much more often (77% of treatments) than surgery (59%).

TABLE 19 Baseline characteristics of study leg: comparison of surgery against foam sclerotherapy

Study leg vein characteristics	Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	286			289		
Study leg						
Right (*N*, *n*, %)	286	136	47.6	289	138	47.8
Left (*N*, *n*, %)	286	150	52.4	289	151	52.2
Saphenous involvement						
GSV only (*N*, *n*, %)	286	232	81.1	289	239	82.7
Widest diameter (mm) (*n*, mean, range)	211	8.4	4–15	214	8.7	3–15
Reflux above knee only (*N*, *n*, %)	180	169	93.9	183	180	98.4
Reflux above and below knee (*N*, *n*, %)	180	11	6.1	183	3	1.6
SSV only (*N*, *n*, %)	286	21	7.3	289	21	7.3
Widest diameter (mm) (*n*, mean, range)	20	7.6	3–11	17	7.7	4–15
GSV and SSV (*N*, *n*, %)	286	33	11.5	289	29	10.0
Widest diameter GSV (mm) (*n*, mean, range)	31	7.3	3–14	28	7.6	3–15
Widest diameter SSV (mm) (*n*, mean, range)	30	5.0	3–10	26	5.4	3–8
Reflux above knee only (*N*, *n*, %)	26	11	42.3	22	10	45.5
Reflux above and below knee (*N*, *n*, %)	26	15	57.7	22	12	54.5
Deep-vein reflux (*N*, *n*, %)	280	47	16.8	282	25	8.9
CEAP classification						
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	286	0	0.0	287	0	0.0
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	286	0	0.0	287	0	0.0
C2 Varicose veins > 3 mm (*N*, *n*, %)	286	169	59.1	287	147	51.2
C3 Oedema (*N*, *n*, %)	286	35	12.2	287	39	13.6
C4 Skin and subcutaneous changes (*N*, *n*, %)	286	30	10.5	287	32	11.1
C4a Pigmentation or eczema (*N*, *n*, %)	286	41	14.3	287	55	19.2
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	286	3	1.0	287	3	1.0
C5 Healed venous ulcer (*N*, *n*, %)	286	4	1.4	287	7	2.4
C6 Active venous ulcer (*N*, *n*, %)	286	4	1.4	287	4	1.4
VCSS (*n*, mean, SD)	285	4.9	2.6	286	5.1	2.5
Presence of varicose veins						
Assessed by participant (*N*, *n*, %)	286	286	100	289	288	99.7
VAS (*n*, mean, SD)	286	5.4	2.2	289	5.6	2.3
Assessed by research nurse (*N*, *n*, %)	286	286	100	289	288	99.7
VAS (*n*, mean, SD)	286	3.9	2.1	289	4.0	2.2

TABLE 20 Baseline characteristics of contralateral leg in patients who had bilateral varicose veins: comparison of surgery against foam sclerotherapy

Non-study leg vein characteristics	Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	286			289		
Participants with bilateral disease (*N*, *n*, %)	286	71	24.8	289	93	32.5
CEAP classification						
C2 Varicose veins > 3 mm (*N*, *n*, %)	68	49	72.1	90	50	55.6
C3 Oedema (*N*, *n*, %)	68	8	11.8	90	15	16.7
C4 Skin and subcutaneous changes (*N*, *n*, %)	68	3	4.4	90	9	10.0
C4a Pigmentation or eczema (*N*, *n*, %)	68	6	8.8	90	15	16.7
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	68	0	0.0	90	0	0.0
C5 Healed venous ulcer (*N*, *n*, %)	68	2	2.9	90	0	0.0
C6 Active venous ulcer (*N*, *n*, %)	68	0	0.0	90	1	1.1
VCSS (*N*, mean, SD)	67	3.8	2.4	88	3.9	2.2

TABLE 21 Description of primary interventions: comparison of surgery against foam sclerotherapy

Primary intervention	Randomised to foam sclerotherapy			Randomised to surgery		
Treated (*n*)	275			267		
Received foam (*N*, *n*, %)	275	265	96.4	267	7	2.6
Received surgery (*N*, *n*, %)	275	4	1.5	267	252	94.4
Received laser (*N*, *n*, %)	275	6	2.2	267	8	3.0
Treatment time (minutes) (*n*, mean, SD)	248	19.0	10.6	247	53.0	22.9
Grade of surgeon						
Consultant (*N*, *n*, %)	271	208	76.8	261	153	58.6
Consultant nurse (*N*, *n*, %)	271	33	12.2	261	3	1.1
Staff grade (supervised) (*N*, *n*, %)	271	3	1.1	261	14	5.4
Staff grade (unsupervised) (*N*, *n*, %)	271	2	0.7	261	8	3.1
Trainee (supervised) (*N*, *n*, %)	271	14	5.2	261	42	16.1
Trainee (unsupervised) (*N*, *n*, %)	271	11	4.1	261	41	15.7
Treatment to non-truncal varicosities (*N*, *n*, %)	270	84	31.1	260	233	89.6
Concurrent contralateral treatment (*N*, *n*, %)	269	7	2.6	261	40	15.3
Subcutaneous heparin (or derivative) (*N*, *n*, %)	262	13	5.0	238	115	48.3
Overnight hospitalisation						
Planned (*N*, *n*, %)	268	0	0.0	203	8	3.9
Unplanned (*N*, *n*, %)	268	0	0.0	203	5	2.5
Bandaging not according to protocol (*N*, *n*, %)	272	103[a]	37.9	256	29	11.3
Recommended duration of bandaging (if not for 10 days) (*n*, mean, SD)	10	6.8	0.6	27	6.7	3.2

a For all but 10 of these, the deviation from protocol was in relation to the specific bandaging/compression used rather than the duration of bandaging.

Only 8% of foam participants received treatment from a trainee, compared with 32% in the surgery group. The remainder of procedures were performed by staff grades or nurse consultants. Nearly all patients (98%) randomised to surgery had a general anaesthetic, with six receiving an epidural/spinal anaesthetic (*Table 22*). The anaesthetist was a consultant in 83% of cases.

Primary treatment volume of foam

The total mean volume of foam administered was 9.0 ml (SD 2.9 ml). When the GSV alone was treated, the mean volume was 9.2 ml (SD 2.9 ml), with 8 ml (SD 3.0 ml) to the truncal vein and 1.2 ml (SD 2.2 ml) to the truncal varicosities (*Table 23*). There were six patients who received foam in excess of the 12-ml limit recommended in the protocol, without adverse consequences.

TABLE 22 Description of anaesthetic

Anaesthetic details	Randomised to foam sclerotherapy[a]			Randomised to surgery		
Received surgery (*n*)	4			252		
Type of anaesthetic						
General (*N*, *n*, %)	4	4	100.0	248	242	97.6
Epidural/spinal (*N*, *n*, %)	4	0	0.0	248	6	2.4
Grade of anaesthetist						
Consultant (*N*, *n*, %)	4	3	75.0	245	204	83.3
Associate specialist (*N*, *n*, %)	4	0	0.0	245	5	2.0
Registrar (*N*, *n*, %)	4	1	25.0	245	27	11.0
Staff grade (*N*, *n*, %)	4	0	0.0	245	9	3.7
Senior house officer (*N*, *n*, %)	4	0	0.0	245	0	0.0

a Patients randomised to foam sclerotherapy, but underwent surgery as their primary treatment.

TABLE 23 Volume of foam administered at primary treatment

Primary foam treatment	Randomised to foam sclerotherapy			Randomised to surgery[a]		
Received primary treatment of foam (*n*)	265			7		
Volume of foam (ml) (*n*, mean, range)	265	9.0	2–15	7	8.3	6–10
GSV involvement only (total) (*n*, mean, range)	215	9.2	2–15	5	7.6	6–10
GSV (*n*, mean, range)	215	8.0	0–15	5	6.8	6–8
Non-truncal varicosities (*n*, mean, range)	215	1.2	0–12	5	0.8	0–4
SSV involvement only (total) (*n*, mean, range)	20	6.8	2–12	1	10.0	10–10
SSV (*n*, mean, range)	20	5.4	0–12	1	10.0	10–10
Non-truncal varicosities (*n*, mean, range)	20	1.4	0–6	1	0.0	0–0
GSV and SSV involvement (total) (*n*, mean, range)	30	9.0	6–13	1	10.0	10–10
GSV (*n*, mean, range)	30	6.8	2–12	1	6.0	6–6
SSV (*n*, mean, range)	30	0.7	0–5	1	0.0	0–0
Non-truncal varicosities (*n*, mean, range)	30	1.4	0–6	1	4.0	4–4

a Patients randomised to surgery but received foam sclerotherapy as their primary treatment.

Secondary or tertiary foam treatments

The numbers of participants who received secondary or tertiary treatments of foam sclerotherapy, along with a breakdown of the location of treatment, is shown in *Table 24*. Seventeen participants randomised to foam sclerotherapy (7%) received additional foam treatment to non-truncal varicosities, compared with one randomised to surgery (1%). There were two participants whose second foam treatment included foam sclerotherapy to the GSV and also to non-truncal varicosities. The one participant who received a tertiary treatment had treatment to both the SSV and GSV.

Bandaging/compression

All participants had a bandage or stocking applied to their study leg, nearly all of which were full length. More foam participants (38%) than surgery participants (11%) received bandaging not according to protocol (see *Table 21*). The main reason for this difference was that the protocol specified the brand of bandaging/compression for patients undergoing foam sclerotherapy, whereas, for surgery, any type of bandaging for 10 days was sufficient. Of the 103 cases of foam participants whose bandaging was not according to protocol, only 10 were related to duration and the other 93 were related to the type of stockings.

Treatment outcome: quality of life

The QoL at 6 weeks and 6-months follow-up are shown in *Tables 25* and *26*, with the corresponding statistical analysis in *Table 27*.

Aberdeen Varicose Vein Questionnaire

At 6 weeks and 6 months, all QoL measures showed an apparent improvement compared with baseline. The treatment effect estimate for AVVQ (our primary outcome) at 6 weeks was −2.26 (95% CI −3.67 to −0.86, $p = 0.002$) in favour of surgery and at 6 months the estimate was −1.74 (95% CI −2.97 to −0.50, $p = 0.006$).

TABLE 24 Secondary foam treatment

Secondary foam treatment	Randomised to foam sclerotherapy			Randomised to surgery[a]		
No secondary foam treatment (*N*, *n*, %)	251	224	89.2	236	233	98.7
One secondary foam treatment (*N*, *n*, %)	251	26	10.4	236	3	1.3
to GSV (*N*, *n*, %)	251	9	3.6	236	1	0.4
to SSV (*N*, *n*, %)	251	2	0.8	236	1	0.4
to non-truncal varicosities (*N*, *n*, %)	251	17	6.8	236	1	0.4
Two secondary foam treatments (*N*, *n*, %)	251	1	0.4	236	0	0.0
to GSV (*N*, *n*, %)	251	1	0.4	236	0	0.0
to SSV (*N*, *n*, %)	251	1	0.4	236	0	0.0
to non-truncal varicosities (*N*, *n*, %)	251	0	0.0	236	0	0.0

a Patients randomised to surgery but received foam sclerotherapy as their primary treatment.

TABLE 25 Quality of life at 6 weeks following treatment: comparison of surgery with foam sclerotherapy

QoL measure	Randomised to foam sclerotherapy			Randomised to surgery		
Completed 6-weeks questionnaire (*N*, *n*, %)	286	247	86.4	289	237	82.0
AVVQ score (*n*, mean, SD)	246	12.2	9.6	235	10.6	8.8
EQ-5D score (*n*, mean, SD)	242	0.86	0.16	227	0.88	0.17
VAS (*n*, mean, SD)	244	80.6	17.3	232	83.1	15.5
SF-36 summary scores						
Physical component summary score (*n*, mean, SD)	242	49.9	8.7	226	49.7	8.9
Mental component summary score (*n*, mean, SD)	242	52.3	9.0	226	51.7	8.9
SF-36 domain scores						
Physical functioning (*n*, mean, SD)	245	50.8	8.9	235	51.5	8.1
Role physical (*n*, mean, SD)	246	50.3	9.6	235	48.1	10.3
Bodily pain (*n*, mean, SD)	244	50.2	9.2	229	49.1	10.1
General health (*n*, mean, SD)	245	50.8	9.0	232	52.2	8.9
Vitality (*n*, mean, SD)	245	52.3	9.7	232	51.7	9.3
Social functioning (*n*, mean, SD)	243	51.1	8.9	230	50.2	9.5
Role emotional (*n*, mean, SD)	246	51.2	8.6	234	50.0	10.4
Mental health (*n*, mean, SD)	245	52.5	8.8	232	52.3	9.0

TABLE 26 Quality of life at 6 months following treatment: comparison of surgery with foam sclerotherapy

QoL measure	Randomised to foam sclerotherapy			Randomised to surgery		
Completed 6-months questionnaire (N, *n*, %)	286	238	83.2	289	214	74.0
AVVQ score (*n*, mean, SD)	236	9.1	7.9	213	7.8	7.5
EQ-5D score (*n*, mean, SD)	235	0.90	0.17	206	0.88	0.20
VAS (*n*, mean, SD)	237	84.5	12.3	210	82.8	15.3
SF-36 summary scores						
Physical component summary score (*n*, mean, SD)	232	52.3	8.5	204	52.4	8.9
Mental component summary score (*n*, mean, SD)	232	52.2	9.1	204	52.1	8.6
SF-36 domain scores						
Physical functioning (*n*, mean, SD)	237	52.0	7.9	213	51.5	8.8
Role physical (*n*, mean, SD)	236	52.3	8.1	213	51.9	8.7
Bodily pain (*n*, mean, SD)	235	53.0	9.5	209	53.7	10.0
General health (*n*, mean, SD)	238	51.8	8.7	212	51.9	9.6
Vitality (*n*, mean, SD)	238	53.0	9.6	212	53.0	9.7
Social functioning (*n*, mean, SD)	235	52.6	8.2	211	51.9	9.0
Role emotional (*n*, mean, SD)	237	51.5	8.8	211	51.5	9.3
Mental health (*n*, mean, SD)	238	52.5	9.2	212	51.8	9.3

TABLE 27 Estimates of the effect of treatment on QoL: comparison of surgery with foam sclerotherapy

	Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. foam sclerotherapy		
QoL measure	*n*	Mean	SD	*n*	Mean	SD	Effect size[a]	95% CI	*p*-value
AVVQ score at baseline	286	17.6	9.9	289	18.2	9.1	N/A	N/A	N/A
AVVQ score at 6 weeks	246	12.2	9.6	235	10.6	8.8	–2.26	–3.67 to –0.86	0.002
AVVQ score at 6 months	236	9.1	7.9	213	7.8	7.5	–1.74	–2.97 to –0.50	0.006
EQ-5D at baseline	286	0.80	0.18	289	0.78	0.17	N/A	N/A	N/A
EQ-5D at 6 weeks	242	0.86	0.16	227	0.88	0.17	0.02	0.00 to 0.05	0.071
EQ-5D at 6 months	235	0.90	0.17	206	0.88	0.20	0.01	–0.02 to 0.04	0.732
EQ-5D VAS at baseline	286	80.8	15.5	289	80.2	15.5	N/A	N/A	N/A
EQ-5D VAS at 6 weeks	244	80.6	17.3	232	83.1	15.5	2.90	0.31 to 5.48	0.028
EQ-5D VAS at 6 months	237	84.5	12.3	210	82.8	15.3	–1.23	–3.42 to 0.96	0.270
SF-36 physical component score at baseline	286	48.9	8.0	289	48.2	8.6	N/A	N/A	N/A
SF-36 physical component score at 6 weeks	242	49.9	8.7	226	49.7	8.9	0.27	–1.03 to 1.56	0.687
SF-36 physical component score at 6 months	232	52.3	8.5	204	52.4	8.9	1.03	–0.25 to 2.30	0.114
SF-36 mental component score at baseline	286	52.4	8.7	289	51.2	9.4	N/A	N/A	N/A
SF-36 mental component score at 6 weeks	242	52.3	9.0	226	51.7	8.9	–0.44	–1.82 to 0.93	0.527
SF-36 mental component score at 6 months	232	52.2	9.1	204	52.1	8.6	0.23	–1.10 to 1.56	0.738
SF-36 Physical functioning at baseline	286	50.1	8.7	289	50.1	8.2	N/A	N/A	N/A
SF-36 Physical functioning at 6 weeks	245	50.8	8.9	235	51.5	8.1	0.60	–0.58 to 1.77	0.320
SF-36 Physical functioning at 6 months	237	52.0	7.9	213	51.5	8.8	–0.28	–1.39 to 0.84	0.625
SF-36 Role physical at baseline	286	50.6	8.6	289	49.1	9.9	N/A	N/A	N/A
SF-36 Role physical at 6 weeks	246	50.3	9.6	235	48.1	10.3	–1.56	–3.14 to 0.02	0.053
SF-36 Role physical at 6 months	236	52.3	8.1	213	51.9	8.7	0.65	–0.53 to 1.83	0.278

continued

TABLE 27 Estimates of the effect of treatment on QoL: comparison of surgery with foam sclerotherapy (*continued*)

	Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. foam sclerotherapy		
QoL measure	*n*	Mean	SD	*n*	Mean	SD	Effect size[a]	95% CI	*p*-value
SF-36 Bodily pain at baseline	286	48.1	8.8	289	46.3	9.2	N/A	N/A	N/A
SF-36 Bodily pain at 6 weeks	244	50.2	9.2	229	49.1	10.1	–0.39	–1.97 to 1.19	0.627
SF-36 Bodily pain at 6 months	235	53.0	9.5	209	53.7	10.0	1.95	0.42 to 3.47	0.012
SF-36 General health at baseline	286	49.8	7.9	289	49.2	8.8	N/A	N/A	N/A
SF-36 General health at 6 weeks	245	50.8	9.0	232	52.2	8.9	1.63	0.41 to 2.85	0.009
SF-36 General health at 6 months	238	51.8	8.7	212	51.9	9.6	0.46	–0.82 to 1.75	0.480
SF-36 Vitality at baseline	286	51.6	9.5	289	50.8	9.4	N/A	N/A	N/A
SF-36 Vitality at 6 weeks	245	52.3	9.7	232	51.7	9.3	–0.35	–1.72 to 1.01	0.611
SF-36 Vitality at 6 months	238	53.0	9.6	212	53.0	9.7	0.37	–0.96 to 1.69	0.589
SF-36 Social functioning at baseline	286	51.5	8.1	289	49.8	9.8	N/A	N/A	N/A
SF-36 Social functioning at 6 weeks	243	51.1	8.9	230	50.2	9.5	–0.25	–1.70 to 1.21	0.742
SF-36 Social functioning at 6 months	235	52.6	8.2	211	51.9	9.0	0.38	–0.89 to 1.65	0.554
SF-36 Role emotional at baseline	286	51.3	8.2	289	50.5	9.4	N/A	N/A	N/A
SF-36 Role emotional at 6 weeks	246	51.2	8.6	234	50.0	10.4	–1.06	–2.57 to 0.44	0.164
SF-36 Role emotional at 6 months	237	51.5	8.8	211	51.5	9.3	0.49	–0.95 to 1.92	0.505
SF-36 Mental health at baseline	286	52.1	9.2	289	51.0	9.7	N/A	N/A	N/A
SF-36 Mental health at 6 weeks	245	52.5	8.8	232	52.3	9.0	0.10	–1.23 to 1.42	0.888
SF-36 Mental health at 6 months	238	52.5	9.2	212	51.8	9.3	–0.04	–1.40 to 1.32	0.956

N/A, not applicable.

a If the effect size is negative for the AVVQ score or positive for EQ-5D, EQ-5D VAS or SF-36, this indicates an effect which favours surgery.

Sensitivity analyses

There were some missing AVVQ scores at 6 months (26% for the surgery arm and 17% for foam). Exploratory analysis shows that participants without a valid AVVQ score at 6 months had mean baseline AVVQ scores of 18.3 (SD 11.4) for foam and 18.2 (SD 10.3) for surgery. Those with an AVVQ score at 6 months had mean baseline scores of 17.4 (SD 9.7) for foam and 18.2 (SD 8.8) for surgery, indicating that there are differences in the missing data between groups. The mean AVVQ score at 6 weeks for participants with missing scores at 6 months is 11.8 for foam (slightly lower than the mean for all foam participants) and 7.7 for surgery (much lower than the mean for all surgery participants), which suggests that the treatment effect of –1.74 in favour of surgery may be underestimated in the primary analysis.

Table 28 demonstrates different estimates of the effect of treatment on the primary outcome when all missing AVVQ scores at 6 months have been imputed under varying assumptions. Under the 'missing not at random' assumption, the estimate of treatment effect is –2.00 (95% CI –3.30 to –0.70). Variously adding or subtracting two points to or from these imputed values, for either one arm at a time or both arms simultaneously, the resulting estimates range from –1.47 to –2.52, all significantly in favour of surgery. The missing AVVQ values for surgery would need to be at least 2.7 points higher (or the missing values for foam 4.0 points lower) than the imputed values for the difference between the groups to be non-significant.

Short Form questionnaire-36 items

There were no differences between foam and surgery for the overall physical and mental component scores or individual domains of the SF-36.

European Quality of Life-5 Dimensions

There were no differences in the EQ-5D or EQ-5D VAS between the foam and surgery groups.

Clinical outcomes

Venous Clinical Severity Score and presence of residual varicose veins

These outcomes at 6 weeks and 6 months are presented in *Tables 29* and *30* respectively, with the estimates of treatment effect sizes when surgery is compared with foam shown in *Table 31*.

Each outcome showed an apparent improvement in both groups from baseline to 6 weeks and from 6 weeks to 6 months. The VCSS was significantly lower for surgery than for foam after 6 weeks, with an effect size of –0.52 (95% CI –0.85 to –0.19, $p = 0.002$). However, there was no difference between groups at 6 months, when the effect size reduced (–0.23, 95% CI –0.53 to 0.07; $p = 0.130$).

TABLE 28 Sensitivity of estimates of the effect of treatment on the AVVQ score at 6 months (primary outcome) using other missing data assumptions: comparison of surgery with foam sclerotherapy

Sensitivity analysis	Effect size[a]	95% CI	*p*-value
Primary analysis (repeated measures, assuming missing at random)	–1.74	–2.97 to –0.50	0.006
Multiple imputation (assuming missing not at random)	–2.00	–3.30 to –0.70	0.003
All missing assumed to have AVVQ scores two points lower	–2.17	–3.48 to –0.86	0.001
All missing assumed to have AVVQ scores two points higher	–1.82	–3.12 to –0.52	0.006
Missing in foam group assumed to have AVVQ scores two points lower	–1.65	–2.95 to –0.35	0.014
Missing in foam group assumed to have AVVQ scores two points higher	–2.35	–3.65 to –1.05	0.001
Missing in surgery group assumed to have AVVQ scores two points lower	–2.52	–3.83 to –1.22	< 0.001
Missing in surgery group assumed to have AVVQ scores two points higher	–1.47	–2.77 to –0.17	0.027

a Where the effect size is negative, this favours surgery.

TABLE 29 Clinical outcomes for study leg at 6 weeks: comparison of surgery with foam sclerotherapy

Clinical outcome measure	Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 weeks (*N*, *n*, %)	286	265	92.7	289	251	86.9
VCSS (*n*, mean, SD)	251	2.2	2.0	230	1.8	2.0
Presence of residual varicosities						
Assessed by participant (*N*, *n*, %)	261	221	84.7	242	173	71.5
VAS (*n*, mean, SD)	261	2.6	2.0	242	1.7	1.8
Assessed by research nurse (*N*, *n*, %)	261	197	75.5	242	125	51.7
VAS (*n*, mean, SD)	261	1.7	1.6	242	0.8	1.0
CEAP classification						
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	253	54	21.3	229	80	34.9
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	253	74	29.2	229	92	40.2
C2 Varicose veins > 3 mm (*N*, *n*, %)	253	92	36.4	229	33	14.4
C3 Oedema (*N*, *n*, %)	253	9	3.6	229	2	0.9
C4 Skin and subcutaneous changes (*N*, *n*, %)	253	6	2.4	229	6	2.6
C4a Pigmentation or eczema (*N*, *n*, %)	253	16	6.3	229	13	5.7
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	253	1	0.4	229	1	0.4
C5 Healed venous ulcer (*N*, *n*, %)	253	1	0.4	229	2	0.9
C6 Active venous ulcer (*N*, *n*, %)	253	0	0.0	229	0	0.0

TABLE 30 Clinical outcomes for study leg at 6 months: comparison of surgery with foam sclerotherapy

Clinical outcome measure	Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 months (*N*, *n*, %)	286	251	87.8	289	236	81.7
VCSS (*n*, mean, SD)	221	1.6	1.7	205	1.4	1.7
Presence of residual varicosities						
Assessed by participant (*N*, *n*, %)	232	190	81.9	224	146	65.2
VAS (*n*, mean, SD)	232	2.3	1.9	224	1.4	1.6
Assessed by research nurse (*N*, *n*, %)	232	149	64.2	224	110	49.1
VAS (*n*, mean, SD)	232	1.2	1.3	224	0.7	1.0
CEAP classification						
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	222	60	27.0	212	74	34.9
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	222	81	36.5	212	85	40.1
C2 Varicose veins > 3 mm (*N*, *n*, %)	222	53	23.9	212	31	14.6
C3 Oedema (*N*, *n*, %)	222	11	5.0	212	3	1.4
C4 Skin and subcutaneous changes (*N*, *n*, %)	222	0	0.0	212	4	1.9
C4a Pigmentation or eczema (*N*, *n*, %)	222	15	6.8	212	12	5.7
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	222	1	0.5	212	1	0.5
C5 Healed venous ulcer (*N*, *n*, %)	222	1	0.5	212	2	0.9
C6 Active venous ulcer (*N*, *n*, %)	222	0	0.0	212	0	0.0

TABLE 31 Estimates of the effect of treatment on clinical outcomes: comparison of surgery with foam sclerotherapy

	Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. foam[a]		
Sensitivity analysis	*n*	Mean	SD	*n*	Mean	SD	Effect size	95% CI	*p*-value
VCSS at baseline	286	4.9	2.6	289	5.1	2.5	N/A	N/A	N/A
VCSS at 6 weeks	251	2.2	2.0	230	1.8	2.0	–0.52	–0.85 to –0.19	0.002
VCSS at 6 months	221	1.6	1.7	205	1.4	1.7	–0.23	–0.53 to 0.07	0.130
Patient VAS[b] at baseline	286	5.4	2.2	289	5.6	2.3	N/A	N/A	N/A
Patient VAS[b] at 6 weeks	261	2.6	2.0	242	1.7	1.8	–0.99	–1.31 to –0.68	< 0.001
Patient VAS[b] at 6 months	232	2.3	1.9	224	1.4	1.6	–0.95	–1.27 to –0.63	< 0.001
Nurse VAS[c] at baseline	286	3.9	2.1	289	4.0	2.2	N/A	N/A	N/A
Nurse VAS[c] at 6 weeks	261	1.7	1.6	242	0.8	1.0	–0.87	–1.09 to –0.65	< 0.001
Nurse VAS[c] at 6 months	232	1.2	1.3	224	0.7	1.0	–0.50	–0.71 to –0.30	< 0.001

N/A, not applicable.
a Where the effect size is negative, this favours surgery.
b Patient assessment of presence of varicose veins/residual varicosities.
c Nurse assessment of presence of varicose veins/residual varicosities.

Both the participant and nurse assessments (as assessed by the VAS) showed that there were fewer residual varicose veins for surgery than for foam at both follow-up time points [$p < 0.001$ (patient at 6 weeks –0.99, 95% CI –1.31 to –0.68, and at 6 months –0.95, 95% CI –1.27 to –0.63; nurse at 6 weeks –0.87, 95% CI –1.09 to –0.65, and at 6 months –0.50, 95% CI –0.71 to –0.30)].

The CEAP classification is presented for completeness, although it is generally accepted that this should not be used as a measure of treatment outcome.[72] By 6 months, 75% of those in the surgery arm were classed as CEAP C0 or C1, compared with 64% of those in the foam sclerotherapy arm.

Ablation rates

These are shown in *Tables 32* and *33* for 6 weeks and 6 months respectively. The overall statistical analyses for the whole leg and the GSV only are shown in *Table 34*. The number of participants undergoing treatment to the SSV alone or in combination with the GSV was small, and therefore these subgroups were not subjected to statistical analysis.

For the whole leg, the rate of successful ablation was significantly higher in the surgery group than in the foam sclerotherapy group at 6 weeks and 6 months (6 months OR 3.37, 95% CI 2.26 to 5.02; $p < 0.001$). Similar results were obtained for treatment to the GSV only at both time points (6 months OR 4.94, 95% CI 3.07 to 7.93; $p < 0.001$).

Pain

Immediately after treatment, the mean pain score for those randomised to surgery was 2.4 (SD 2.6) compared with 2.2 (SD 2.0) for those randomised to foam sclerotherapy (see *Appendix 2*, *Table 106*). At 6 weeks, the patients' recollection of pain during treatment was higher than that recorded after treatment, and appeared to be higher for those randomised to surgery than for those randomised to foam sclerotherapy [4 (SD 3.0) vs. 3 (SD 2.4)]. The patients' recollection of pain during recovery also appeared higher in the surgery group [4.3 (SD 2.8) vs. 3 (SD 2.4)].

TABLE 32 Anatomical success at 6 weeks: comparison of surgery with foam sclerotherapy

Anatomical success	Randomised to foam sclerotherapy			Randomised to surgery		
Duplex assessment at 6 weeks (*N*, *n*, %)	286	265	92.7	289	251	86.9
GSV involvement only						
Complete success (*N*, *n*, %)	205	112	54.6	192	162	84.4
Partial success (*N*, *n*, %)	205	56	27.3	192	21	10.9
without reflux (*N*, *n*, %)	205	47	22.9	192	12	6.3
with reflux (*N*, *n*, %)	205	9	4.4	192	9	4.7
Failure (*N*, *n*, %)	205	37	18.0	192	9	4.7
SSV involvement only						
Complete success (*N*, *n*, %)	16	9	56.3	17	5	29.4
Partial success (*N*, *n*, %)	16	5	31.3	17	9	52.9
without reflux (*N*, *n*, %)	16	5	31.3	17	7	41.2
with reflux (*N*, *n*, %)	16	0	0.0	17	2	11.8
Failure (*N*, *n*, %)	16	2	12.5	17	3	17.6
GSV and SSV involvement *GSV*						
Complete success (*N*, *n*, %)	29	13	44.8	25	20	80.0
Partial success (*N*, *n*, %)	29	8	27.6	25	3	12.0
without reflux (*N*, *n*, %)	29	6	20.7	25	3	12.0
with reflux (*N*, *n*, %)	29	1	3.4	25	0	0.0
Failure (*N*, *n*, %)	29	8	27.6	25	2	8.0
SSV						
Complete success (*N*, *n*, %)	27	5	18.5	23	2	8.7
Partial success (*N*, *n*, %)	27	4	14.8	23	5	21.7
without reflux (*N*, *n*, %)	27	3	11.1	23	2	8.7
with reflux (*N*, *n*, %)	27	0	0.0	23	3	13.0
Failure (*N*, *n*, %)	27	18	66.7	23	16	69.6
Overall treatment of study leg						
Complete success (*N*, *n*, %)	246	125	50.8	230	167	72.6
Partial success (*N*, *n*, %)	246	77	31.3	230	51	22.2
without reflux (*N*, *n*, %)	246	64	26.0	230	34	14.8
with reflux (*N*, *n*, %)	246	13	5.3	230	17	7.4
Failure (*N*, *n*, %)	246	44	17.9	230	12	5.2

TABLE 33 Anatomical success at 6 months: comparison of surgery with foam sclerotherapy

Anatomical success	Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 months (*N*, *n*, %)	286	251	87.8	289	236	81.7
GSV involvement only						
Complete success (*N*, *n*, %)	182	79	43.4	173	135	78.0
Partial success (*N*, *n*, %)	182	44	24.2	173	24	13.9
without reflux (*N*, *n*, %)	182	35	19.2	173	4	2.3
with reflux (*N*, *n*, %)	182	9	4.9	173	20	11.6
Failure (*N*, *n*, %)	182	59	32.4	173	14	8.1
SSV involvement only						
Complete success (*N*, *n*, %)	17	7	41.2	14	4	28.6
Partial success (*N*, *n*, %)	17	3	17.6	14	4	28.6
without reflux (*N*, *n*, %)	17	2	11.8	14	4	28.6
with reflux (*N*, *n*, %)	17	1	5.9	14	0	0.0
Failure (*N*, *n*, %)	17	7	41.2	14	6	42.9
GSV and SSV involvement *GSV*						
Complete success (*N*, *n*, %)	26	6	23.1	21	16	76.2
Partial success (*N*, *n*, %)	26	7	26.9	21	2	9.5
without reflux (*N*, *n*, %)	26	6	23.1	21	1	4.8
with reflux (*N*, *n*, %)	26	1	3.8	21	1	4.8
Failure (*N*, *n*, %)	26	13	50.0	21	3	14.3
SSV						
Complete success (*N*, *n*, %)	23	3	13.0	20	2	10.0
Partial success (*N*, *n*, %)	23	2	8.7	20	1	5.0
without reflux (*N*, *n*, %)	23	2	8.7	20	1	5.0
with reflux (*N*, *n*, %)	23	0	0.0	20	0	0.0
Failure (*N*, *n*, %)	23	18	78.3	20	17	85.0
Overall treatment of study leg						
Complete success (*N*, *n*, %)	221	89	40.3	206	139	67.5
Partial success (*N*, *n*, %)	221	59	26.7	206	45	21.8
without reflux (*N*, *n*, %)	221	49	22.2	206	25	12.1
with reflux (*N*, *n*, %)	221	10	4.5	206	20	9.7
Failure (*N*, *n*, %)	221	73	33.0	206	22	10.7

TABLE 34 Estimates of the effect of treatment on anatomical success: comparison of surgery with foam sclerotherapy

	Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. foam[a]		
Sensitivity analysis	*N*	*n*	%	*N*	*n*	%	OR	95% CI	*p*-value
Truncal vein ablation									
Complete success at 6 weeks (whole leg)	246	125	50.8	230	167	72.6			
Partial success without reflux at 6 weeks (whole leg)	246	64	26.0	230	34	14.8			
Partial success with reflux at 6 weeks (whole leg)	246	13	5.3	230	17	7.4			
Failure at 6 weeks (whole leg)	246	44	17.9	230	12	5.2	3.07	2.05 to 4.59	< 0.001
Complete success at 6 months (whole leg)	221	89	40.3	206	139	67.5			
Partial success without reflux at 6 months (whole leg)	221	49	22.2	206	25	12.1			
Partial success with reflux at 6 months (whole leg)	221	10	4.5	206	20	9.7			
Failure at 6 months (whole leg)	221	73	33.0	206	22	10.7	3.37	2.26 to 5.02	< 0.001
Complete success at 6 weeks (GSV)	205	112	54.6	192	162	84.4			
Partial success without reflux at 6 weeks (GSV)	205	47	22.9	192	12	6.3			
Partial success with reflux at 6 weeks (GSV)	205	9	4.4	192	9	4.7			
Failure at 6 weeks (GSV)	205	37	18.0	192	9	4.7	5.12	3.09 to 8.48	< 0.001
Complete success at 6 months (GSV)	182	79	43.4	173	135	78.0			
Partial success without reflux at 6 months (GSV)	182	35	19.2	173	4	2.3			
Partial success with reflux at 6 months (GSV)	182	9	4.9	173	20	11.6			
Failure at 6 months (GSV)	182	59	32.4	173	14	8.1	4.94	3.07 to 7.93	< 0.001

a An OR of > 1 favours surgery.

Complications

Procedural complications

The event rate for any complication was similar in both groups (6% for foam and 7% for surgery) (*Table 35*). Six participants in the foam group (2%) and three in the surgery group (1%) each experienced two complications. In patients randomised to surgery, 2.5% had an unscheduled overnight admission following their treatment (see *Table 21*).

TABLE 35 Procedural complications at time of primary treatment: comparison of surgery with foam sclerotherapy

Procedural complication	Randomised to foam sclerotherapy			Randomised to surgery		
Treated (*n*)	275			267		
Any procedural complication[a] (*N*, *n*, %)	275	17	6.2	267	19	7.1
Wound haematoma (*N*, *n*, %)	275	1	0.4	267	1	0.4
Damage to major artery (*N*, *n*, %)	275	0	0.0	267	0	0.0
Damage to major vein (*N*, *n*, %)	275	0	0.0	267	0	0.0
Damage to major nerve (*N*, *n*, %)	275	0	0.0	267	0	0.0
Bleeding (*N*, *n*, %)	275	0	0.0	267	2	0.7
Visual disturbance/blurred vision (*N*, *n*, %)	275	4	1.5	267	0	0.0
Extravasation of foam sclerotherapy (*N*, *n*, %)	275	0	0.0	267	1	0.4
Allergic/anaphylactoid reaction (*N*, *n*, %)	275	0	0.0	267	0	0.0
Stroke (*N*, *n*, %)	275	0	0.0	267	0	0.0
Transient ischaemic attack (*N*, *n*, %)	275	0	0.0	267	0	0.0
Myocardial infarction (*N*, *n*, %)	275	0	0.0	267	0	0.0
Intra-arterial injection (*N*, *n*, %)	275	0	0.0	267	0	0.0
Epileptic fit (*N*, *n*, %)	275	0	0.0	267	0	0.0
Headache (*N*, *n*, %)	275	2	0.7	267	1	0.4
Transient confusion (*N*, *n*, %)	275	0	0.0	267	0	0.0
Panic attack (*N*, *n*, %)	275	1	0.4	267	0	0.0
Malaise (*N*, *n*, %)	275	0	0.0	267	0	0.0
Cough (*N*, *n*, %)	275	1	0.4	267	0	0.0
Chest tightness/heaviness (*N*, *n*, %)	275	2	0.7	267	0	0.0
Vasovagal (*N*, *n*, %)	275	3	1.1	267	1	0.4
Anaesthetic side effects (*N*, *n*, %)	275	0	0.0	267	7	2.6
Sickness (*N*, *n*, %)	275	0	0.0	267	4	1.5
Muscle pains (*N*, *n*, %)	275	0	0.0	267	1	0.4
Sore throat (*N*, *n*, %)	275	0	0.0	267	3	1.1
Damage to teeth, lip or tongue (*N*, *n*, %)	275	0	0.0	267	0	0.0
Other procedural complication (*N*, *n*, %)	275	9	3.3	267	8	3.0

a Some participants experienced more than one procedural complication.

Later complications

Complications recorded at the time of the 6-week and 6-month assessments are shown in *Tables 36* and *37*. Estimates of the effect of treatment on complications are summarised across both follow-up time points in *Table 38*, with ORs comparing surgery with foam sclerotherapy. The overall complication rate was lower for surgery than for foam sclerotherapy at 6 weeks (OR 0.40, 95% CI 0.26 to 0.62; $p < 0.001$) and at 6 months (OR 0.64, 95% CI 0.44 to 0.92; $p = 0.015$).

TABLE 36 Complications at 6 weeks: comparison of surgery with foam sclerotherapy

Complication	Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 weeks (*N*, *n*, %)	286	265	92.7	289	251	86.9
Any complication at 6 weeks (*N*, *n*, %)	265	219	82.6	251	168	66.9
Numbness (*N*, *n*, %)	265	15	5.7	251	45	17.9
Persistent bruising (*N*, *n*, %)	265	49	18.5	251	32	12.7
Persist tenderness/discomfort (*N*, *n*, %)	265	122	46.0	251	79	31.5
Skin loss/ulceration (*N*, *n*, %)	265	2	0.8	251	1	0.4
Lumpiness (*N*, *n*, %)	265	171	64.5	251	83	33.1
Development of thread vein (*N*, *n*, %)	265	27	10.2	251	21	8.4
Skin staining (*N*, *n*, %)	265	105	39.6	251	20	8.0
Wound infection (*N*, *n*, %)	265	2	0.8	251	23	9.2
Backache (*N*, *n*, %)	265	5	1.9	251	9	3.6
Headache (*N*, *n*, %)	265	13	4.9	251	4	1.6
DVT (*N*, *n*, %)	265	3	1.1	251	0	0.0
Pulmonary embolus (*N*, *n*, %)	265	0	0.0	251	0	0.0
Stroke (*N*, *n*, %)	265	0	0.0	251	0	0.0
Myocardial infarction (*N*, *n*, %)	265	0	0.0	251	0	0.0
Loss of vision (*N*, *n*, %)	265	4	1.5	251	0	0.0
Damage to major artery (*N*, *n*, %)	265	0	0.0	251	0	0.0
Damage to major vein (*N*, *n*, %)	265	1	0.4	251	0	0.0
Damage to motor nerve (*N*, *n*, %)	265	0	0.0	251	0	0.0
Other complication (*N*, *n*, %)	265	16	6.0	251	20	8.0

TABLE 37 Complications at 6 months: comparison of surgery with foam sclerotherapy

Complication	Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 months (*N*, *n*, %)	286	251	87.8	289	236	81.6
Any complication at 6 months (*N*, *n*, %)	251	144	57.4	236	109	46.2
Numbness (*N*, *n*, %)	251	10	4.0	236	37	15.6
Persistent bruising (*N*, *n*, %)	251	38	15.2	236	40	17.0
Skin loss/ulceration (*N*, *n*, %)	251	2	0.8	236	0	0.0
Lumpiness (*N*, *n*, %)	251	67	26.6	236	17	7.2
Development of thread vein (*N*, *n*, %)	251	34	13.6	236	26	11.0
Skin staining (*N*, *n*, %)	251	92	36.6	236	24	10.2
DVT (*N*, *n*, %)	251	2	0.8	236	0	0.0
Pulmonary embolus (*N*, *n*, %)	251	0	0.0	236	0	0.0
Other (*N*, *n*, %)	251	8	3.2	236	12	5.0

TABLE 38 Estimates of the effect of treatment on complications: comparison of surgery with foam sclerotherapy

	Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. foam[a]		
Complication type	*N*	*n*	%	*N*	*n*	%	OR	95% CI	*p*-value
Procedural complications at time of treatment	275	17	6.2	267	19	7.1	1.07	0.55 to 2.09	0.848
Any complication at 6 weeks	265	219	82.6	251	168	66.9	0.40	0.26 to 0.62	< 0.001
Any complication at 6 months	251	144	57.4	236	109	46.2	0.64	0.44 to 0.92	0.015
Numbness at 6 weeks	265	15	5.7	251	45	17.9	3.98	2.11 to 7.50	< 0.001
Numbness at 6 months	251	10	4.0	236	37	15.6	5.39	2.50 to 11.62	< 0.001
Persistent bruising at 6 weeks	265	49	18.5	251	32	12.7	0.63	0.37 to 1.06	0.080
Persistent bruising at 6 months	251	38	15.2	236	40	17.0	1.16	0.70 to 1.92	0.576
Persist tenderness/discomfort at 6 weeks	265	122	46.0	251	79	31.5	0.52	0.36 to 0.77	0.001
Skin loss/ulceration at 6 weeks	265	2	0.8	251	1	0.4	0.64	0.04 to 10.32	0.750
Skin loss/ulceration at 6 months	251	2	0.8	236	0	0.0	N/C	N/C	N/C
Lumpiness at 6 weeks	265	171	64.5	251	83	33.1	0.23	0.15 to 0.34	< 0.001
Lumpiness at 6 months	251	67	26.6	236	17	7.2	0.18	0.10 to 0.33	< 0.001
Development of thread vein at 6 weeks	265	27	10.2	251	21	8.4	0.75	0.40 to 1.40	0.364
Development of thread vein at 6 months	251	34	13.6	236	26	11.0	0.78	0.44 to 1.38	0.390
Skin staining at 6 weeks	265	105	39.6	251	20	8.0	0.12	0.07 to 0.21	< 0.001
Skin staining at 6 months	251	92	36.6	236	24	10.2	0.16	0.10 to 0.28	< 0.001
Backache at 6 weeks	265	5	1.9	251	9	3.6	2.16	0.67 to 6.95	0.198
Headache at 6 weeks	265	13	4.9	251	4	1.6	0.31	0.10 to 0.98	0.047

N/C, not calculable.
a An OR of > 1 favours foam sclerotherapy; an OR of < 1 favours surgery.

The event rates for cutaneous numbness (6 weeks OR 3.98, 95% CI 2.11 to 7.50; $p < 0.001$, and 6 months OR 5.39, 95% CI 2.50 to 11.62; $p < 0.001$) were significantly higher for surgery than for foam sclerotherapy. Wound infection occurred in 9.2% of the surgical patients at 6 weeks – a much higher proportion than the 0.8% of foam patients with wound infection – but clearly this complication only occurred in foam patients who had treatment other than that to which they had been randomised.

However, the rates for lumpiness (6 weeks OR 0.23, 95% CI 0.15 to 0.34; $p < 0.001$, and 6 months OR 0.18, 95% CI 0.10 to 0.33; $p < 0.001$), skin staining (6 weeks OR 0.12, 95% CI 0.07 to 0.21; $p < 0.001$, and 6 months OR 0.16, 95% CI 0.10 to 0.28; $p < 0.001$), persistent tenderness (6 weeks OR 0.52, 95% CI 0.36 to 0.77; $p = 0.001$) and headache (6 weeks OR 0.31, 95% CI 0.10 to 0.98; $p = 0.047$) were all significantly higher for foam sclerotherapy than for surgery. There were no differences for persistent bruising, skin loss/ulceration or development of thread vein at either time point. There was also no difference for backache at 6 weeks. At 6 months, data on wound infection, persistent tenderness, backache and headache were not collected.

Serious adverse events

Eleven SAEs were noted among those randomised to foam. Among these were three DVTs; all were assessed as related to treatment and expected. The other eight SAEs were not related to the foam treatment; full details are given in *Table 39*. Ten SAEs were noted among those randomised to surgery. Four of these (groin infection, post-operative infection, post-operative haematoma, injury to peroneal nerve) were assessed as being related to treatment. The other six SAEs were not related to treatment (see *Table 39*).

TABLE 39 Serious adverse events detected up to the time of the 6-months follow-up

Randomised	Treatment prior to SAE	Description of event	Related to treatment?	Expected?
Foam	Foam	DVT (non-occlusive tongue of thrombus extending from the SFJ to the common femoral vein); asymptomatic	Yes	Yes
Foam	Foam	Thrombophlebitis extending through the perforator mid-/proximal calf causing small DVT in the medial gastrocnemius vein	Yes	Yes
Foam	Foam	DVT (involving < 20% of lumen) in the right common femoral vein (asymptomatic)	Yes	Yes
Foam	Foam	Possible transient ischaemic attack. CT scan has shown ill-defined areas in subcortical white matter in both hemispheres; unclear if ischaemia or demyelinating	No	Yes
Foam	Foam	Headache associated with pre-syncope and vomiting (history of migraine with hemiplegia)	No	Yes
Foam	No treatment	Prior to treatment experienced right hemisphere cerebrovascular accident (stroke)	No	Yes
Foam	No treatment	Provisional diagnosis of myeloma	No	No
Foam	Foam	Chest pain – thought to be musculoskeletal	No	No
Foam	Foam	Urinary retention following elective laparoscopic left inguinal hernia repair	No	No
Foam	Foam	Breast cancer	No	No
Foam	Foam	Road traffic accident – no spinal or bony injury	No	No
Surgery	Surgery	Groin infection requiring further surgery for evacuation of haematoma	Yes	Yes
Surgery	Surgery	Injury to motor nerve (peroneal); presumably as a result of trauma during phlebectomies	Yes	Yes
Surgery	Surgery	Post-operative haematoma; deranged liver function tests	Yes	Yes
Surgery	Surgery	Post-operative infection – abscess to left calf; abscess of the pilonidal sinus	Yes	Yes
Surgery	Surgery	Surgery to wrong vein	No	No
Surgery	Surgery	Sectioned under the Mental Health Act	No	No
Surgery	Surgery	Road traffic accident – suffered right shoulder and neck pain	No	No
Surgery	Surgery	Endoscopic excision of an anal polyp	No	No
Surgery	Surgery	Acute upper-left quadrant pain – likely to have been caused by gall stone and cholecystitis	No	No
Surgery	Surgery	Breast enlargement	No	No

CT, computerised tomography.

Process evaluation: Illness Perception Questionnaire – Revised

Detailed descriptive results of the IPQ-R are given in *Appendix 2* (see *Table 108*). There is little change in either randomised group in mean identity scores or the percentage of symptoms correctly identified as being related to varicose veins between baseline (recruitment) and after the participant is informed of his or her randomisation. The scores in each randomised group were similar at both time points. By 6 months, both measures of illness identity had fallen.

There is little difference between baseline and post-randomisation scores for all other domains. Scores were also similar between randomised groups at baseline and post treatment. Personal control and illness coherence scores increased marginally between baseline and 6 months; all other domain scores fell within this time scale.

Chapter 6 Comparison of surgery, endovenous laser ablation and foam sclerotherapy

This chapter reports the results of the three-arm comparison of surgery, EVLA and foam sclerotherapy, using data from the eight centres which randomised participants to all three treatment groups. This chapter will focus on comparing surgery with EVLA, and EVLA with foam sclerotherapy. Comparisons between foam sclerotherapy and surgery have been made using data from all centres and are reported in *Chapter 5*. A discussion of the results presented in this chapter is included in *Chapter 7*.

Participants

Six hundred and thirty-six participants were randomised in the three-arm centres, of which there were six post-randomisation exclusions, leaving a total of 630 participants included in this analysis (207 in the foam sclerotherapy arm, 213 in the surgery arm and 210 in the EVLA arm). The CONSORT diagram (see *Figure 2*) describes the flow of participants in the trial.

The proportion receiving treatment as allocated appeared to be higher for EVLA (97%) than for foam sclerotherapy (91%) and surgery (85%). Retention appeared to be lower for surgery, both for the follow-up clinic assessments and completion of participant questionnaires, than for foam sclerotherapy and EVLA. The 6-weeks clinic was attended by 85% of participants randomised to surgery compared with 91% for foam sclerotherapy and 92% for EVLA. At the 6-months follow-up, the attendance rates were 78%, 86% and 87% for surgery, foam sclerotherapy and EVLA respectively.

The 6-weeks questionnaire was completed by 81% of participants randomised to surgery compared with 88% for foam sclerotherapy and 89% for EVLA. At 6 months, the questionnaires were completed by 74%, 82% and 83% of participants for surgery, foam sclerotherapy and EVLA respectively. The largest proportion of withdrawals from the study at 6 months was in the surgery arm (13%), compared with foam sclerotherapy (7%) and EVLA (4%).

Baseline characteristics

Demographic details

The baseline characteristics of study participants are shown in *Table 40*. There was a good balance between groups for most factors, particularly for age and sex, which were minimisation variables. There was a slight imbalance between groups in terms of bilateral disease. The data shown in *Table 11* were also used in the analysis when adjusting for minimisation factors.

Quality of life

At baseline, the QoL for the surgery group appeared slightly worse than for the other two groups, and this was reflected in the AVVQ score, EQ-5D and each of the SF-36 components and domain scores (*Table 41*). The mean baseline AVVQ score was 18.1 (SD 9.1) for surgery, 17.8 (SD 9.1) for EVLA and 17.4 (SD 9.7) for foam (a higher AVVQ score indicates worse QoL).

TABLE 40 Baseline characteristics of study participants: comparison of EVLA with foam sclerotherapy and surgery with EVLA

Participant characteristics	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	210			207			213		
Age (*n*, mean, range)	210	49.7	18–80	207	48.3	19–78	213	48.4	22–85
Female (*N*, *n*, %)	210	120	57.1	207	119	57.5	213	121	56.8
BMI (kg/m^2) (*n*, mean, range)	195	27.0	17–42	192	27.1	17–44	188	27.8	20–44
Employment status									
Self-employed (*N*, *n*, %)	206	21	10.2	206	20	9.7	206	20	9.7
Employed (*N*, *n*, %)	206	120	58.3	206	123	59.7	206	138	67.0
Other (*N*, *n*, %)	206	65	31.6	206	63	30.6	206	48	23.3
Laterality									
Unilateral (*N*, *n*, %)	210	153	72.9	207	157	75.8	213	148	69.5
Bilateral (*N*, *n*, %)	210	57	27.1	207	50	24.2	213	65	30.5
Previous history of DVT (*N*, *n*, %)	206	6	2.9	205	2	1.0	210	7	3.3
Previous treatment to contralateral leg (*N*, *n*, %)	208	27	13.0	205	22	10.7	211	20	9.5
Foam sclerotherapy (*N*, *n*, %)	208	4	1.9	205	6	2.9	211	1	0.5
Surgery (*N*, *n*, %)	208	19	9.1	205	16	7.8	211	16	7.6
EVLA (*N*, *n*, %)	208	3	1.4	205	0	0.0	211	3	1.4
Previous sclerotherapy to tributaries of study leg (*N*, *n*, %)	208	3	1.4	205	0	0.0	211	3	1.4

TABLE 41 Quality of life at baseline: comparison of EVLA with foam sclerotherapy and surgery with EVLA

QoL measure	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	210			207			213		
AVVQ score (*n*, mean, SD)	210	17.8	9.1	206	17.4	9.7	210	18.1	9.1
EQ-5D score (*n*, mean, SD)	206	0.79	0.17	202	0.79	0.19	207	0.78	0.18
VAS (*n*, mean, SD)	206	80.6	16.3	205	80.6	16.3	210	80.0	15.5
SF-36 summary scores									
Physical component summary score (*n*, mean, SD)	204	48.6	7.9	199	48.4	8.7	202	48.2	9.0
Mental component summary score (*n*, mean, SD)	204	51.9	9.1	199	51.8	9.2	202	50.8	9.9
SF-36 subscale scores									
Physical functioning (*n*, mean, SD)	208	50.2	8.3	205	49.8	8.6	207	50.0	8.5
Role physical (*n*, mean, SD)	208	50.1	8.3	206	50.2	9.1	207	49.0	10.1
Bodily pain (*n*, mean, SD)	207	47.3	8.5	206	47.6	9.2	208	46.0	9.7
General health (*n*, mean, SD)	209	49.5	8.3	202	49.1	8.4	210	49.2	8.7
Vitality (*n*, mean, SD)	210	51.5	9.2	206	51.1	9.8	209	50.2	9.5
Social functioning (*n*, mean, SD)	207	50.8	8.9	205	50.9	8.4	209	49.8	9.9
Role emotional (*n*, mean, SD)	208	51.1	8.4	205	51.0	8.8	206	50.1	10.0
Mental health (*n*, mean, SD)	209	51.6	9.2	206	51.3	9.6	208	50.7	10.2

Physical activity

There was a good balance between the groups in terms of physical activity at baseline (*Table 42*).

Varicose vein characteristics

Tables 43 and *44* show the baseline characteristics of the varicose veins in the study leg and the contralateral leg. The groups are well balanced across the majority of factors (except for deep-vein reflux, where the rate was 18% for foam, 14% for EVLA and 9% for surgery).

TABLE 42 Physical activity at baseline: comparison of EVLA with foam sclerotherapy and surgery with EVLA

Physical activity	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	210			207			213		
Physical activity at work									
Mostly sitting (*N*, *n*, %)	202	27	13.4	201	30	14.9	205	30	14.6
Mostly standing or walking (*N*, *n*, %)	202	47	23.3	201	60	29.9	205	58	28.3
Definite physical effort (*N*, *n*, %)	202	52	25.7	201	43	21.4	205	62	30.2
Vigorous physical effort (*N*, *n*, %)	202	16	7.9	201	11	5.5	205	9	4.4
Not in employment (*N*, *n*, %)	202	60	29.7	201	57	28.4	205	46	22.4
Physical activity in previous week									
Physical activities (*N*, *n*, %)	204	95	46.6	205	93	45.4	206	94	45.6
Cycling (*N*, *n*, %)	197	32	16.2	201	23	11.4	202	38	18.8
Walking (*N*, *n*, %)	204	202	99.0	206	201	97.6	204	199	97.5
Housework/childcare (*N*, *n*, %)	203	177	87.2	205	186	90.7	204	178	87.3
Gardening (*N*, *n*, %)	203	114	56.2	204	130	63.7	203	118	58.1
Usual walking pace									
Slow (*N*, *n*, %)	205	17	8.3	204	12	5.9	207	14	6.8
Steady/average (*N*, *n*, %)	205	101	49.3	204	103	50.5	207	111	53.6
Brisk (*N*, *n*, %)	205	72	35.1	204	78	38.2	207	67	32.4
Fast (*N*, *n*, %)	205	15	7.3	204	11	5.4	207	15	7.2

TABLE 43 Baseline characteristics of study leg: comparison of EVLA with foam sclerotherapy and surgery with EVLA

Study leg vein characteristics	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	210			207			213		
Study leg									
Right (*N*, *n*, %)	210	108	51.4	207	103	49.8	213	101	47.4
Left (*N*, *n*, %)	210	102	48.6	207	104	50.2	213	112	52.6
Saphenous involvement									
GSV only (*N*, *n*, %)	210	182	86.7	207	175	84.5	213	184	86.4
Widest diameter (mm) (*n*, mean, range)	162	9.1	3–15	154	8.2	4–15	159	8.6	4–15
Reflux above knee only (*N*, *n*, %)	157	151	96.2	146	138	94.5	152	150	98.7
Reflux above and below knee (*N*, *n*, %)	157	6	3.8	146	8	5.5	152	2	1.3
SSV only (*N*, *n*, %)	210	14	6.7	207	14	6.8	213	16	7.5
Widest diameter (mm) (*n*, mean, range)	13	7.1	5–10	13	6.8	3–10	12	7.8	4–15
GSV and SSV (*N*, *n*, %)	210	14	6.7	207	18	8.7	213	13	6.1
Widest diameter: GSV (mm) (*n*, mean, range)	13	6.3	4–15	16	7.5	4–14	12	7.6	3–15
Widest diameter: SSV (mm) (*n*, mean, range)	10	6.8	3–15	15	4.9	3–10	11	5.1	3–7
Reflux above knee only (*N*, *n*, %)	12	6	50.0	13	7	53.8	9	5	55.6
Reflux above and below knee (*N*, *n*, %)	12	6	50.0	13	6	46.2	9	4	44.4
Deep-vein reflux (*N*, *n*, %)	205	28	13.7	201	36	17.9	207	19	9.2
CEAP classification									
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	209	0	0.0	207	0	0.0	211	0	0.0
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	209	0	0.0	207	0	0.0	211	0	0.0
C2 Varicose veins > 3 mm (*N*, *n*, %)	209	113	54.1	207	122	58.9	211	107	50.7
C3 Oedema (*N*, *n*, %)	209	28	13.4	207	28	13.5	211	29	13.7
C4 Skin and subcutaneous changes (*N*, *n*, %)	209	17	8.1	207	21	10.1	211	28	13.3
C4a Pigmentation or eczema (*N*, *n*, %)	209	34	16.3	207	29	14.0	211	38	18.0
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	209	5	2.4	207	2	1.0	211	0	0.0
C5 Healed venous ulcer (*N*, *n*, %)	209	9	4.3	207	3	1.4	211	5	2.4
C6 Active venous ulcer (*N*, *n*, %)	209	3	1.4	207	2	1.0	211	4	1.9
VCSS (*n*, mean, SD)	207	5.0	2.5	206	4.8	2.5	210	5.0	2.4
Presence of varicose veins									
Assessed by participant (*N*, *n*, %)	210	209	99.5	207	207	100	213	213	100
VAS (*n*, mean, SD)	210	5.5	2.3	207	5.2	2.2	213	5.6	2.3
Assessed by research nurse (*N*, *n*, %)	210	210	100	207	207	100	213	212	99.5
VAS (*n*, mean, SD)	210	3.6	2.2	207	3.6	2.1	213	3.7	2.3

TABLE 44 Baseline characteristics of contralateral leg: comparison of EVLA with foam sclerotherapy and surgery with EVLA

Non-study leg vein characteristics	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Randomised (*n*)	210			207			213		
Participants with bilateral disease (*N*, *n*, %)	210	57	27.1	207	50	24.2	213	65	30.5
CEAP classification									
C2 Varicose veins > 3 mm (*N*, *n*, %)	55	36	65.5	47	30	63.8	62	31	50.0
C3 Oedema (*N*, *n*, %)	55	8	14.5	47	7	14.9	62	10	16.1
C4 Skin and subcutaneous changes (*N*, *n*, %)	55	4	7.3	47	3	6.4	62	7	11.3
C4a Pigmentation or eczema (*N*, *n*, %)	55	6	10.9	47	6	12.8	62	13	21.0
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	55	1	1.8	47	0	0.0	62	0	0.0
C5 Healed venous ulcer (*N*, *n*, %)	55	0	0.0	47	1	2.1	62	0	0.0
C6 Active venous ulcer (*N*, *n*, %)	55	0	0.0	47	0	0.0	62	1	1.6
VCSS (*n*, mean, SD)	54	3.6	2.3	46	4.1	2.4	61	4.2	2.4

Treatment received

Tables 45–48 summarise the primary interventions received (i.e. excluding any delayed secondary foam treatments). For participants randomised to EVLA, 99% of those who received treatment had their treatment as randomised. The equivalent proportions were 95% and 93% in the foam sclerotherapy and surgery arms respectively. Details of those not receiving their randomised intervention are given in *Chapter 4*.

Procedure and treatment time

Treatment to non-truncal varicosities at the time of the primary intervention was performed in 87% of patients in the surgery arm, 30% in the foam sclerotherapy arm and 80% in the one study site in which concurrent EVLA and phlebectomies were performed (Hull). In all other centres, patients who were randomised to EVLA underwent delayed treatment as required, either at or after the 6-weeks follow-up, as stipulated in the protocol. Fewer patients in the foam arm (3%) appeared to have their contralateral leg treated at the same time than in the surgery (12%) and EVLA (10%) arms.

The mean treatment duration (the time taken from preparation of the patient to completion of bandaging) was shortest for those randomised to foam sclerotherapy (18.9, SD 10.2, minutes) (see *Table 45*). This compares to the other, far longer procedures for surgery (mean duration 51.5, SD 22.9, minutes) and EVLA (45.9, SD 24.6, minutes). Fewer consultants and more trainees performed surgery compared with the other treatments. Fifty-two per cent of surgery participants received treatment from a consultant surgeon, compared with 79% in the foam sclerotherapy group and 73% in the EVLA group. Trainees performed 38% of treatments in the surgical group, 23% in the EVLA group and 10% in the foam sclerotherapy group. The remainder of procedures were performed by the nurse consultants or staff grades.

Nearly all patients in the surgery group (97%) had a general anaesthetic, with five receiving an epidural/spinal anaesthetic (see *Table 46*). The anaesthetist was a consultant in 82% of cases.

TABLE 45 Description of primary interventions: comparison of EVLA with foam sclerotherapy and surgery with EVLA

Primary intervention	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Treated (*n*)	205			197			195		
Received foam (*N*, *n*, %)	205	0	0.0	197	188	95.4	195	5	2.6
Received surgery (*N*, *n*, %)	205	2	1.0	197	3	1.5	195	182	93.3
Received EVLA (*N*, *n*, %)	205	203	99.0	197	6	3.0	195	8	4.1
Treatment time (minutes) (*n*, mean, SD)	189	45.9	24.6	174	18.9	10.2	178	51.5	22.9
Grade of surgeon									
Consultant (*N*, *n*, %)	201	146	72.6	195	154	79.0	190	99	52.1
Consultant nurse (*N*, *n*, %)	201	0	0.0	195	16	8.2	190	3	1.6
Staff grade (supervised) (*N*, *n*, %)	201	1	0.5	195	3	1.5	190	10	5.3
Staff grade (unsupervised) (*N*, *n*, %)	201	7	3.5	195	2	1.0	190	6	3.2
Trainee (supervised) (*N*, *n*, %)	201	15	7.5	195	11	5.6	190	35	18.4
Trainee (unsupervised) (*N*, *n*, %)	201	32	15.9	195	9	4.6	190	37	19.5
Treatment to non-truncal varicosities (*N*, *n*, %)	61[a]	49	80.3	192	57	29.7	188	163	86.7
Concurrent contralateral treatment (*N*, *n*, %)	203	20	9.9	193	6	3.1	192	23	12.0
Subcutaneous heparin (or derivative) (*N*, *n*, %)	202	14	6.9	186	13	7.0	181	72	39.8
Overnight hospitalisation									
Planned (*N*, *n*, %)	197	0	0.0	190	0	0.0	161	6	3.7
Unplanned (*N*, *n*, %)	197	0	0.0	190	0	0.0	161	5	3.1
Bandaging not according to protocol (*N*, *n*, %)	194	18	9.3	194	101[b]	52.1	185	23	12.4
Recommended duration of bandaging (if not for 10 days) (*n*, mean, SD)	17	7.4	1.7	9	7.0	0.0	21	7.2	2.5

a Treatment to non-truncal varicosities at the same time as EVLA was only offered in one site.
b The majority of these deviations from protocol occurred because the types of bandages and stockings described in the protocol were not available in the site.

TABLE 46 Description of anaesthetic

Anaesthetic details	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Received surgery (*N*, *n*, %)	2[a]			3[b]			182		
Type of anaesthetic									
General (*N*, *n*, %)	2	2	100.0	3	3	100.0	179	174	97.2
Epidural/spinal (*N*, *n*, %)	2	0	0.0	3	0	0.0	179	5	2.8
Grade of anaesthetist									
Consultant (*N*, *n*, %)	2	1	50.0	3	2	66.7	176	145	82.4
Associate specialist (*N*, *n*, %)	2	1	50.0	3	0	0.0	176	2	1.1
Registrar (*N*, *n*, %)	2	0	0.0	3	1	33.3	176	25	14.2
Staff grade (*N*, *n*, %)	2	0	0.0	3	0	0.0	176	4	2.3
Senior house officer (*N*, *n*, %)	2	0	0.0	3	0	0.0	176	0	0.0

a Randomised to EVLA but received surgery.
b Randomised to foam but received surgery.

TABLE 47 Additional description of EVLA

EVLA details	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Received EVLA (*n*)	203			6			8		
GSV involvement only									
Watts (*n*, mean, range)	168	13.8	7–30	2	13.0	12–14	5	13.6	12–14
Length (cm) (*n*, mean, range)	172	40.9	12–79	2	23.5	21–26	7	36.6	21–54
J/cm (*n*, mean, range)	170	82.5	40–188	2	71.9	67–77	6	71.6	59–91
Wavelength									
810 nm (*N*, *n*, %)	134	90	67.2	1	1	100.0	5	4	80.0
1064 nm (*N*, *n*, %)	134	10	7.5	1	0	0.0	5	0	0.0
1470 nm (*N*, *n*, %)	134	34	25.4	1	0	0.0	5	1	20.0
SSV involvement only									
Watts (*n*, mean, range)	13	12.4	7–14	0	N/A	N/A	1	14.0	N/A
Length (cm) (*n*, mean, range)	13	19.4	7–45	0	N/A	N/A	1	12.0	N/A
J/cm (*n*, mean, range)	12	77.5	53–114	0	N/A	N/A	1	75.1	N/A
Wavelength									
810 nm (*N*, *n*, %)	10	7	70.0	0	N/A	N/A	1	1	100.0
1064 nm (*N*, *n*, %)	10	0	0.0	0	N/A	N/A	1	0	0.0
1470 nm (*N*, *n*, %)	10	3	30.0	0	N/A	N/A	1	0	0.0
GSV and SSV involvement									
Watts (GSV) (*n*, mean, range)	9	17.6	10–30	0	N/A	N/A	0	N/A	N/A
Length (cm) (GSV) (*n*, mean, range)	9	39.8	27–56	0	N/A	N/A	0	N/A	N/A
J/cm (GSV) (*n*, mean, range)	9	100.3	61–165	0	N/A	N/A	0	N/A	N/A
Wavelength (GSV)									
810 nm (*N*, *n*, %)	9	3	33.3	0	N/A	N/A	0	N/A	N/A
1064 nm (*N*, *n*, %)	9	3	33.3	0	N/A	N/A	0	N/A	N/A
1470 nm (*N*, *n*, %)	9	3	33.3	0	N/A	N/A	0	N/A	N/A
Watts (SSV) (*n*, mean, range)	5	9.6	7–14	0	N/A	N/A	0	N/A	N/A
Length (cm) (SSV) (*n*, mean, range)	5	15.6	5–26	0	N/A	N/A	0	N/A	N/A
J/cm (SSV) (*n*, mean, range)	5	63.7	36–82	0	N/A	N/A	0	N/A	N/A
Wavelength (SSV)									
810 nm (*N*, *n*, %)	3	2	66.7	0	N/A	N/A	0	N/A	N/A
1064 nm (*N*, *n*, %)	3	0	0.0	0	N/A	N/A	0	N/A	N/A
1470 nm (*N*, *n*, %)	3	1	33.3	0	N/A	N/A	0	N/A	N/A
Foam sclerotherapy to incompetent distal GSV at time of (or immediately following) EVLA treatment (*N*, *n*, %)	203	0	0.0	6	0	0.0	8	0	0.0

N/A, not applicable.

TABLE 48 Volume of foam administered at primary treatment of foam

Primary foam treatment	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Received primary treatment of foam (*n*)	0			188			5[a]		
Volume of foam (ml) (*n*, mean, range)	0	N/A	N/A	188	9.1	2–15	5	7.6	6–10
GSV involvement only (total) (*n*, mean, range)	0	N/A	N/A	158	9.4	2–15	4	7.0	6–8
GSV (*n*, mean, range)	0	N/A	N/A	158	8.2	2–15	4	7.0	6–8
Non-truncal varicosities (*n*, mean, range)	0	N/A	N/A	158	1.2	0–8	4	0.0	0–0
SSV involvement only (total) (*n*, mean, range)	0	N/A	N/A	14	6.4	2–12	1	10.0	10–10
SSV (*n*, mean, range)	0	N/A	N/A	14	5.6	0–12	1	10.0	10–10
Non-truncal varicosities (*n*, mean, range)	0	N/A	N/A	14	0.8	0–5	1	0.0	0–0
GSV and SSV involvement (total) (*n*, mean, range)	0	N/A	N/A	16	9.2	6–13	0	N/A	N/A
GSV (*n*, mean, range)	0	N/A	N/A	16	6.8	3–12	0	N/A	N/A
SSV (*n*, mean, range)	0	N/A	N/A	16	0.7	0–5	0	N/A	N/A
Non-truncal varicosities (*n*, mean, range)	0	N/A	N/A	16	1.7	0–6	0	N/A	N/A

N/A, not applicable.
a Patients randomised to surgery but received alternative treatment.

Endovenous laser ablation treatment

Details specific to EVLA are shown in *Table 47*. Pooled across treatment arms, the mean length for the GSV was 40.5 cm (SD 14.0 cm) and the mean number of joules per centimetre was 82.9 (SD 29.1). The majority of treatments (73%) were given at 14 W with the other treatments being given at 7, 8, 10, 12, 25 or 30 W. The wavelengths used were 810 nm (66%), 1470 nm (26%) and 1064 nm in the remainder.

Primary treatment volume of foam

Among those randomised to foam sclerotherapy, the mean total volume of foam received was 9.1 ml (SD 3.0 ml) (see *Table 48*). In participants receiving treatment to the GSV only, the mean volume of foam used was 9.3 ml (SD 3.0 ml), with 8.2 ml (SD 3.0 ml) injected into the GSV and 1.1 ml (SD 2.1 ml) into non-truncal varicosities (see *Table 48*). There were five patients who received foam in excess of the 12 ml set out in the protocol without adverse complications.

Secondary or tertiary foam sclerotherapy treatment

Table 49 also shows the numbers of participants who received secondary or tertiary treatments of foam sclerotherapy, along with a breakdown of the location of that treatment. Twenty-five foam participants (14%), 42 EVLA participants (31%) and two surgery participants (1%) received secondary or tertiary foam treatments.

Bandaging/compression

All participants had a bandage or stocking applied to their study leg, and nearly all of these were full length. More foam participants (52%) received bandaging not according to protocol than surgery (12%) and EVLA (9%) participants (see *Table 45*). Of the 101 cases of foam participants whose bandaging was not according to protocol, only nine were related to duration and the other 92 were related to the unavailability of the type of bandaging and stocking specified in the protocol.

TABLE 49 Secondary foam treatment: comparison of EVLA with foam sclerotherapy and surgery with EVLA

Secondary foam treatment	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
No secondary foam treatment (*N*, *n*, %)	136	94	69.1	178	153	86.0	167	165	98.8
One secondary foam treatment (*N*, *n*, %)	136	39	28.7	178	24	13.5	167	2[a]	1.2
to GSV (*N*, *n*, %)	136	6	4.4	178	8	4.5	167	0	0.0
to SSV (*N*, *n*, %)	136	1	0.7	178	2	1.1	167	1[a]	0.6
to non-truncal varicosities (*N*, *n*, %)	136	34	25.0	178	16	9.0	167	1[a]	0.6
Two secondary foam treatments (*N*, *n*, %)	136	3	2.2	178	1	0.6	167	0	0.0
to GSV (*N*, *n*, %)	136	1	0.7	178	1	0.6	167	0	0.0
to SSV (*N*, *n*, %)	136	0	0.0	178	1	0.6	167	0	0.0
to non-truncal varicosities (*N*, *n*, %)	136	3	2.2	178	0	0.0	167	0	0.0

a Patients randomised to surgery but received alternative treatment.

Treatment outcome: quality of life

The QoL at 6-weeks and 6-months follow-up are shown in *Tables 50* and *51*, with the corresponding statistical analysis in *Table 52*.

Aberdeen Varicose Vein Questionnaire

At 6 weeks and 6 months, QoL measures in all treatment groups appeared better than at baseline. There was no significant treatment effect for AVVQ when surgery and EVLA were compared at 6 weeks (0.21, 95% CI −1.38 to 1.79; $p = 0.797$) or at 6 months (−0.63, 95% CI −2.16 to 0.90; $p = 0.419$). The AVVQ was similar for EVLA and foam (at 6 weeks −1.71, 95% CI −3.27 to −0.15; $p = 0.032$, and at 6 months −1.06, 95% CI −2.56 to 0.43; $p = 0.163$).

Sensitivity analyses

There were some missing AVVQ scores at 6 months (27% for surgery and 18% for both EVLA and foam). Exploratory analysis shows that participants without a valid AVVQ score at 6 months had mean baseline AVVQ scores of 18.8 (SD 11.7) for foam sclerotherapy, 18.6 (SD 9.3) for surgery and 20.7 (SD 10.5) for EVLA. Those with an AVVQ score at 6 months had mean baseline scores of 17.1 (SD 9.2) for foam, 17.9 (SD 9.0) for surgery and 17.32 (SD 8.7) for EVLA, indicating that non-respondents had higher mean scores at baseline and that the extent of this difference is not the same in each group (the biggest difference was observed in the EVLA arm). The mean AVVQ score at 6 weeks for participants with missing scores at 6 months is 13.1 (higher than the mean for all EVLA participants), 12.5 for foam sclerotherapy (slightly higher than the mean for all foam participants) and 8.8 for surgery (lower than the mean for all surgery participants), indicating that there are differences in the missing data between groups.

TABLE 50 Quality of life at 6 weeks following treatment: comparison of EVLA with foam sclerotherapy and surgery with EVLA

QoL measure	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Completed 6-weeks questionnaire (*N*, *n*, %)	210	186	88.6	207	183	88.4	213	173	81.2
AVVQ score (*n*, mean, SD)	184	10.6	8.5	183	11.8	8.6	171	11.0	9.2
EQ-5D score (*n*, mean, SD)	184	0.89	0.15	181	0.85	0.17	164	0.86	0.18
VAS (*n*, mean, SD)	185	84.0	14.2	182	80.4	17.1	169	82.5	16.3
SF-36 summary scores									
Physical component summary score (*n*, mean, SD)	181	51.3	7.8	180	49.4	9.0	165	49.1	9.0
Mental component summary score (*n*, mean, SD)	181	53.6	6.9	180	52.3	9.3	165	51.3	9.6
SF-36 subscale scores									
Physical functioning (*n*, mean, SD)	185	52.5	6.8	182	50.3	9.3	171	51.3	8.2
Role physical (*n*, mean, SD)	185	51.9	7.6	183	49.7	10.0	172	47.8	10.5
Bodily pain (*n*, mean, SD)	183	51.4	9.3	181	50.0	9.3	168	48.0	10.2
General health (*n*, mean, SD)	181	51.8	8.2	181	50.3	9.6	169	51.9	9.1
Vitality (*n*, mean, SD)	183	54.3	8.2	181	52.3	9.8	169	50.8	9.5
Social functioning (*n*, mean, SD)	183	52.1	7.2	181	50.9	9.4	168	49.7	10.1
Role emotional (*n*, mean, SD)	185	52.7	7.2	183	51.0	8.8	171	49.9	10.4
Mental health (*n*, mean, SD)	183	54.0	7.3	181	52.3	8.8	169	51.8	9.7

TABLE 51 Quality of life at 6 months following treatment: comparison of EVLA with foam sclerotherapy and surgery with EVLA

QoL measure	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Completed 6-months questionnaire (*N*, *n*, %)	210	175	83.3	207	170	82.1	213	157	73.7
AVVQ score (*n*, mean, SD)	173	7.9	8.4	169	8.9	8.1	156	7.6	7.6
EQ-5D score (*n*, mean, SD)	172	0.90	0.17	167	0.88	0.19	151	0.87	0.21
VAS (*n*, mean, SD)	172	85.1	11.7	169	83.6	13.2	154	82.5	15.1
SF-36 summary scores									
Physical component summary score (*n*, mean, SD)	170	52.6	7.3	167	52.0	9.2	149	51.9	9.4
Mental component summary score (*n*, mean, SD)	170	53.5	7.7	167	51.8	9.7	149	51.7	8.9
SF-36 domain									
Physical functioning (*n*, mean, SD)	174	52.7	6.7	169	51.6	8.4	156	51.0	9.3
Role physical (*n*, mean, SD)	173	52.6	7.4	169	51.9	8.6	157	51.5	8.9
Bodily pain (*n*, mean, SD)	171	54.3	8.9	168	52.9	9.9	152	53.0	10.8
General health (*n*, mean, SD)	173	51.9	9.1	170	51.2	9.2	155	51.6	9.7
Vitality (*n*, mean, SD)	173	54.1	8.5	170	52.7	10.0	155	52.7	9.6
Social functioning (*n*, mean, SD)	173	52.7	7.9	168	52.2	9.0	154	51.5	9.5
Role emotional (*n*, mean, SD)	174	52.5	7.8	169	51.3	9.0	155	51.0	9.8
Mental health (*n*, mean, SD)	173	54.1	7.7	170	51.8	9.9	155	51.4	9.5

TABLE 52 Estimates of the effect of treatment on QoL: comparison of EVLA with foam sclerotherapy and surgery with EVLA

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam sclerotherapy		
QoL measure	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Effect size[a]	95% CI	*p*-value	Effect size[b]	95% CI	*p*-value
AVVQ at baseline	210	17.8	9.1	207	17.4	9.7	213	18.0	9.0	N/A	N/A	N/A	N/A	N/A	N/A
AVVQ at 6 weeks	184	10.6	8.5	183	11.8	8.6	171	11.0	9.2	0.21	–1.38 to 1.79	0.797	–1.71	–3.27 to –0.15	0.032
AVVQ at 6 months	173	7.9	8.4	169	8.9	8.1	156	7.6	7.6	–0.63	–2.16 to 0.90	0.419	–1.06	–2.56 to 0.43	0.163
EQ-5D at baseline	210	0.79	0.17	207	0.79	0.19	213	0.78	0.18	N/A	N/A	N/A	N/A	N/A	N/A
EQ-5D at 6 weeks	184	0.89	0.15	181	0.85	0.17	164	0.86	0.18	–0.02	–0.05 to 0.01	0.126	0.04	0.01 to 0.07	0.004
EQ-5D at 6 months	172	0.90	0.17	167	0.88	0.19	151	0.87	0.21	–0.02	–0.05 to 0.02	0.405	0.02	–0.01 to 0.06	0.164
EQ-5D VAS at baseline	210	80.6	16.1	207	80.6	16.2	213	80.0	15.4	N/A	N/A	N/A	N/A	N/A	N/A
EQ-5D VAS at 6 weeks	185	84.0	14.2	182	80.4	17.1	169	82.5	16.3	–0.90	–3.76 to 1.97	0.539	3.66	0.85 to 6.47	0.011
EQ-5D VAS at 6 months	172	85.1	11.7	169	83.6	13.2	154	82.5	15.1	–2.09	–4.57 to 0.39	0.099	1.70	–0.72 to 4.12	0.167
SF-36 physical component score at baseline	210	48.6	7.8	207	48.4	8.5	213	48.2	8.7	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 physical component score at 6 weeks	181	51.3	7.8	180	49.4	9.0	165	49.1	9.0	–1.75	–3.20 to –0.29	0.019	1.90	0.48 to 3.32	0.009
SF-36 physical component score at 6 months	170	52.6	7.3	167	52.0	9.2	149	51.9	9.4	0.07	–1.41 to 1.55	0.923	0.66	–0.78 to 2.09	0.368
SF-36 mental component score at baseline	210	51.9	9.0	207	51.8	9.0	213	50.9	9.7	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 mental component score at 6 weeks	181	53.6	6.9	180	52.3	9.3	165	51.3	9.6	–1.85	–3.41 to –0.29	0.020	1.11	–0.41 to 2.63	0.151
SF-36 mental component score at 6 months	170	53.5	7.7	167	51.8	9.7	149	51.7	8.9	–1.33	–2.91 to 0.24	0.096	1.54	0.01 to 3.06	0.048

continued

TABLE 52 Estimates of the effect of treatment on QoL: comparison of EVLA with foam sclerotherapy and surgery with EVLA (*continued*)

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam sclerotherapy		
QoL measure	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Effect size[a]	95% CI	*p*-value	Effect size[b]	95% CI	*p*-value
SF-36 Physical functioning at baseline	210	50.2	8.2	207	49.8	8.5	213	50.0	8.4	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Physical functioning at 6 weeks	185	52.5	6.8	182	50.3	9.3	171	51.3	8.2	–0.91	–2.26 to 0.45	0.190	1.82	0.49 to 3.16	0.008
SF-36 Physical functioning at 6 months	174	52.7	6.7	169	51.6	8.4	156	51.0	9.3	–1.03	–2.33 to 0.26	0.117	0.77	–0.50 to 2.03	0.234
SF-36 Role physical at baseline	210	50.1	8.3	207	50.2	9.1	213	49.0	10.0	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Role physical at 6 weeks	185	51.9	7.6	183	49.7	10.0	172	47.8	10.5	–3.48	–5.21 to –1.76	0.000	2.22	0.52 to 3.91	0.010
SF-36 Role physical at 6 months	173	52.6	7.4	169	51.9	8.6	157	51.5	8.9	0.16	–1.22 to 1.54	0.821	0.41	–0.94 to 1.76	0.550
SF-36 Bodily pain at baseline	210	47.3	8.5	207	47.6	9.2	213	46.0	9.5	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Bodily pain at 6 weeks	183	51.4	9.3	181	50.0	9.3	168	48.0	10.2	–2.68	–4.44 to –0.93	0.003	1.64	–0.07 to 3.36	0.061
SF-36 Bodily pain at 6 months	171	54.3	8.9	168	52.9	9.9	152	53.0	10.8	–0.11	–1.92 to 1.71	0.909	1.30	–0.46 to 3.06	0.146
SF-36 General health at baseline	210	49.5	8.3	207	49.1	8.3	213	49.2	8.6	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 General health at 6 weeks	181	51.8	8.2	181	50.3	9.6	169	51.9	9.1	0.33	–1.07 to 1.74	0.641	1.06	–0.32 to 2.45	0.131
SF-36 General health at 6 months	173	51.9	9.1	170	51.2	9.2	155	51.6	9.7	–0.08	–1.60 to 1.44	0.917	0.35	–1.14 to 1.83	0.646
SF-36 Vitality at baseline	210	51.5	9.2	207	51.1	9.7	213	50.2	9.4	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Vitality at 6 weeks	183	54.3	8.2	181	52.3	9.8	169	50.8	9.5	–2.33	–3.88 to –0.78	0.003	1.41	–0.11 to 2.92	0.069

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam sclerotherapy		
QoL measure	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Effect size[a]	95% CI	*p*-value	Effect size[b]	95% CI	*p*-value
SF-36 Vitality at 6 months	173	54.1	8.5	170	52.7	10.0	155	52.7	9.6	–0.49	–2.07 to 1.10	0.546	0.90	–0.64 to 2.44	0.253
SF-36 Social functioning at baseline	210	50.8	8.8	207	50.9	8.4	213	49.8	9.8	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Social functioning at 6 weeks	183	52.1	7.2	181	50.9	9.4	168	49.7	10.1	–1.87	–3.49 to –0.24	0.025	1.22	–0.37 to 2.82	0.133
SF-36 Social functioning at 6 months	173	52.7	7.9	168	52.2	9.0	154	51.5	9.5	–0.57	–2.13 to 0.99	0.472	0.64	–0.88 to 2.16	0.412
SF-36 Role emotional at baseline	210	51.1	8.3	207	51.0	8.7	213	50.1	9.8	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Role emotional at 6 weeks	185	52.7	7.2	183	51.0	8.8	171	49.9	10.4	–2.42	–4.05 to –0.80	0.004	1.60	0.00 to 3.19	0.050
SF-36 Role emotional at 6 months	174	52.5	7.8	169	51.3	9.0	155	51.0	9.8	–0.77	–2.39 to 0.85	0.351	0.96	–0.62 to 2.54	0.231
SF-36 Mental health at baseline	210	51.6	9.2	207	51.3	9.6	213	50.7	10.1	N/A	N/A	N/A	N/A	N/A	N/A
SF-36 Mental health at 6 weeks	183	54.0	7.3	181	52.3	8.8	169	51.8	9.7	–1.57	–3.07 to –0.08	0.039	1.26	–0.21 to 2.72	0.092
SF-36 Mental health at 6 months	173	54.1	7.7	170	51.8	9.9	155	51.4	9.5	–2.11	–3.71 to –0.52	0.010	2.06	0.51 to 3.61	0.009

N/A, not applicable.
a If the effect size is negative for the AVVQ score or positive for EQ-5D, EQ-5D VAS or SF-36, this indicates an effect which favours surgery.
b If the effect size is negative for the AVVQ score or positive for EQ-5D, EQ-5D VAS or SF-36, this indicates an effect which favours EVLA.

In *Tables 53* and *54*, different estimates of the effects of treatment on the primary outcome are shown when all missing AVVQ scores at 6 months were imputed under varying assumptions. When surgery is compared against EVLA, using the 'missing not at random' (MNAR) assumption, the estimate of treatment effect is −1.02 (95% CI −2.48 to 0.45, $p = 0.174$), an increase in the effect size estimated in the primary analysis (see *Table 54*). When variously adding or subtracting two points to the imputed values obtained from multiple imputation, either to one arm at a time or to both arms simultaneously, the resulting estimates range from −0.48 to −1.55 and represent an increase in the effect size in all but one instance (but always maintaining the same direction of effect). The missing AVVQ values for surgery would need to be at least 1.7 points lower (or the missing values for EVLA at least 2.6 points higher) than the values imputed under MNAR for there to be a significant difference in favour of surgery.

For the comparison between EVLA and foam, the MNAR estimate of treatment effect is smaller than the primary analysis at −0.56 (95% CI −1.33 to 0.21). Variations to this assumption result in estimates ranging from −0.38 to −0.75, and in all instances represent a decrease in the effect size (but always maintaining the same direction of effect). The missing AVVQ values for EVLA would need to be at least 2.5 points lower (or the missing values for foam at least 2.3 points higher) than the values imputed under MNAR for there to be a significant difference in favour of EVLA.

TABLE 53 Sensitivity of estimates of the effect of treatment on the AVVQ score at 6 months (primary outcome) using other missing data assumptions: comparison of surgery with EVLA

Sensitivity analysis	Effect size[a]	95% CI	*p*-value
Primary analysis (repeated measures, assuming missing at random)	−0.63	−2.16 to 0.90	0.419
Multiple imputation (assuming MNAR)	−1.02	−2.48 to 0.45	0.174
All missing assumed to have AVVQ scores two points lower	−1.20	−2.68 to 0.28	0.111
All missing assumed to have AVVQ scores two points higher	−0.83	−2.30 to 0.64	0.267
Missing in surgery group assumed to have AVVQ scores two points lower	−1.55	−3.03 to −0.08	0.039
Missing in surgery group assumed to have AVVQ scores two points higher	−0.48	−1.94 to 0.99	0.521
Missing in EVLA group assumed to have AVVQ scores two points lower	−0.66	−2.13 to 0.80	0.374
Missing in EVLA group assumed to have AVVQ scores two points higher	−1.37	−2.84 to 0.10	0.068

MNAR, missing not at random.
a Where the effect size is negative, this favours surgery.

TABLE 54 Sensitivity of estimates of the effect of treatment on the AVVQ score at 6 months (primary outcome) using other missing data assumptions: comparison of EVLA with foam sclerotherapy

Sensitivity analysis	Effect size[a]	95% CI	*p*-value
Primary analysis (repeated measures, assuming missing at random)	−1.06	−2.56 to 0.43	0.163
Multiple imputation (assuming MNAR)	−0.56	−1.33 to 0.21	0.153
All missing assumed to have AVVQ scores two points lower	−0.55	−1.32 to 0.22	0.163
All missing assumed to have AVVQ scores two points higher	−0.57	−1.34 to 0.20	0.146
Missing in foam group assumed to have AVVQ scores two points lower	−0.37	−1.14 to 0.40	0.340
Missing in foam group assumed to have AVVQ scores two points higher	−0.75	−1.51 to 0.02	0.058
Missing in EVLA group assumed to have AVVQ scores two points lower	−0.73	−1.50 to 0.04	0.061
Missing in EVLA group assumed to have AVVQ scores two points higher	−0.38	−1.15 to 0.38	0.326

MNAR, missing not at random.
a Where the effect size is negative, this favours EVLA.

Short Form questionnaire-36 items

At 6 weeks and 6 months, QoL measures in all treatment groups appeared better than at baseline (see *Tables 50* and *51*).

Comparison of endovenous laser ablation with foam sclerotherapy

The overall SF-36 physical component score and physical domains were similar in patients who underwent EVLA (see *Table 52*).

The SF-36 mental component score was similar for the EVLA and foam groups at 6 weeks, but at 6 months a greater health gain was obtained with EVLA (1.54, 95% CI 0.01 to 3.06; $p = 0.048$). There were no statistical differences in the mental domain scores.

Comparison of surgery with endovenous laser ablation

There were no statistical differences in the SF-36 component score between surgery and EVLA. The individual domains of role physical, bodily pain, vitality, social functioning and role emotional showed a significant benefit in favour of EVLA at 6 weeks ($p < 0.005$) but not at 6 months.

European Quality of Life-5 Dimensions

At 6 weeks and 6 months, QoL measures in all treatment groups appeared better than at baseline.

Comparison of endovenous laser ablation with foam sclerotherapy

At 6 weeks there was a significantly greater improvement in the EQ-5D score (0.04, 95% CI 0.01 to 0.07; $p = 0.004$) in patients who underwent EVLA than in those who received foam sclerotherapy. This difference was not apparent at 6-months follow-up. There were no differences in the EQ-5D VAS at either time point.

Comparison of surgery with endovenous laser ablation

At 6 weeks and 6 months, no differences were noted in the EQ-5D and EQ-5D VAS scores between patients who received EVLA and those who underwent surgery.

Clinical outcomes

Venous Clinical Severity Score

These outcomes are presented in *Table 55* (for 6 weeks) and *Table 56* (for 6 months), with the estimates of treatment effect sizes for the comparisons of EVLA with surgery and EVLA with foam therapy in *Table 57*.

The VCSS showed an apparent improvement (reduction in score) in all groups from baseline to 6 weeks, and from 6 weeks to 6 months. There were no differences between EVLA and foam or between surgery and EVLA in the VCSS at any time point.

Residual varicose veins

The presence of residual varicose veins as assessed by the participant and the research nurse show an apparent improvement (reduction in score) in all groups from baseline to 6 weeks and from 6 weeks to 6 months.

Comparison of endovenous laser ablation with foam sclerotherapy

There were no differences at 6 weeks between EVLA and foam sclerotherapy. Participants reported significantly fewer residual varicose veins in the EVLA group at 6-months follow-up (−0.54, 95% CI −0.91 to −0.17; $p = 0.005$). There were no differences in the nurse-reported scores.

TABLE 55 Clinical outcomes for study leg at 6 weeks: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Clinical outcome measure	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 weeks (*N*, *n*, %)	210	193	91.9	207	189	91.3	213	180	84.5
VCSS (*n*, mean, SD)	175	1.7	1.7	177	2.2	2.0	163	1.7	1.9
Presence of residual varicosities									
Assessed by participant (*N*, *n*, %)	187	152	81.3	185	154	83.2	173	125	72.3
VAS (*n*, mean, SD)	187	2.2	1.9	185	2.4	2.0	173	1.8	1.9
Assessed by research nurse (*N*, *n*, %)	186	137	73.7	185	129	69.7	173	83	48.0
VAS (*n*, mean, SD)	186	1.5	1.5	185	1.6	1.6	173	0.8	1.0
CEAP classification									
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	176	29	16.5	179	30	16.8	161	49	30.4
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	176	50	28.4	179	55	30.7	161	73	45.3
C2 Varicose veins > 3 mm (*N*, *n*, %)	176	74	42.0	179	76	42.5	161	23	14.3
C3 Oedema (*N*, *n*, %)	176	4	2.3	179	3	1.7	161	1	0.6
C4 Skin and subcutaneous changes (*N*, *n*, %)	176	4	2.3	179	6	3.4	161	5	3.1
C4a Pigmentation or eczema (*N*, *n*, %)	176	11	6.3	179	9	5.0	161	8	5.0
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	176	1	0.6	179	0	0.0	161	1	0.6
C5 Healed venous ulcer (*N*, *n*, %)	176	3	1.7	179	0	0.0	161	1	0.6
C6 Active venous ulcer (*N*, *n*, %)	176	0	0.0	179	0	0.0	161	0	0.0

TABLE 56 Venous Clinical Severity Score and presence of residual varicose veins at 6 months: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Clinical outcome measure	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 months (*N*, *n*, %)	210	183	87.1	207	178	86.0	213	167	78.4
VCSS (*n*, mean, SD)	157	1.4	1.5	152	1.7	1.8	142	1.3	1.5
Presence of residual varicosities									
Assessed by participant (*N*, *n*, %)	168	122	72.6	162	132	81.5	155	101	65.2
VAS (*n*, mean, SD)	168	1.8	1.9	162	2.3	1.9	155	1.4	1.5
Assessed by research nurse (*N*, *n*, %)	167	90	53.9	162	101	62.3	155	73	47.1
VAS (*n*, mean, SD)	167	1.0	1.4	162	1.1	1.3	155	0.7	1.0
CEAP classification									
C0 No visible or palpable signs of venous disease (*N*, *n*, %)	159	31	19.5	153	26	17.0	149	42	28.2
C1 Telangiectasis or reticular veins < 3 mm (*N*, *n*, %)	159	71	44.7	153	65	42.5	149	69	46.3
C2 Varicose veins > 3 mm (*N*, *n*, %)	159	41	25.8	153	45	29.4	149	25	16.8
C3 Oedema (*N*, *n*, %)	159	3	1.9	153	8	5.2	149	1	0.7
C4 Skin and subcutaneous changes (*N*, *n*, %)	159	1	0.6	153	0	0.0	149	3	2.0
C4a Pigmentation or eczema (*N*, *n*, %)	159	7	4.4	153	8	5.2	149	7	4.7
C4b Lipodermatosclerosis or atrophie blanche (*N*, *n*, %)	159	2	1.3	153	0	0.0	149	0	0.0
C5 Healed venous ulcer (*N*, *n*, %)	159	3	1.9	153	1	0.7	149	2	1.3
C6 Active venous ulcer (*N*, *n*, %)	159	0	0.0	153	0	0.0	149	0	0.0

TABLE 57 Estimates of the effect of treatment on clinical outcomes: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam sclerotherapy		
Clinical outcome measure	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Estimate of effect	95% CI	*p*-value	Estimate	95% CI	*p*-value
VCSS at baseline	210	5.0	2.5	207	4.8	2.5	213	5.0	2.4	N/A	N/A	N/A	N/A	N/A	N/A
VCSS at 6 weeks	175	1.7	1.7	177	2.2	2.0	163	1.7	1.9	−0.02	−0.39 to 0.36	0.929	−0.52	−0.89 to −0.15	0.006
VCSS at 6 months	157	1.4	1.5	152	1.7	1.8	142	1.3	1.5	−0.11	−0.46 to 0.25	0.560	−0.26	−0.61 to 0.09	0.148
Patient VAS[a] at baseline	210	5.5	2.3	207	5.2	2.2	213	5.6	2.3	N/A	N/A	N/A	N/A	N/A	N/A
Patient VAS[a] at 6 weeks	187	2.2	1.9	185	2.4	2.0	173	1.8	1.9	−0.41	−0.78 to −0.03	0.035	−0.37	−0.74 to 0.00	0.053
Patient VAS[a] at 6 months	168	1.8	1.9	162	2.3	1.9	155	1.4	1.5	−0.40	−0.78 to −0.02	0.037	−0.54	−0.91 to −0.17	0.005
Nurse VAS[a] at baseline	210	3.6	2.2	207	3.6	2.1	213	3.7	2.3	N/A	N/A	N/A	N/A	N/A	N/A
Nurse VAS[a] at 6 weeks	186	1.5	1.5	185	1.6	1.6	173	0.8	1.0	−0.76	−1.04 to −0.48	< 0.001	−0.07	−0.35 to 0.21	0.614
Nurse VAS[a] at 6 months	167	1.0	1.4	162	1.1	1.3	155	0.7	1.0	−0.28	−0.54 to −0.02	0.037	−0.12	−0.38 to 0.14	0.354

N/A, not applicable.
a VAS used to assess presence of residual varicose veins.

Comparison of surgery with endovenous laser ablation

There were significantly fewer residual varicose veins following surgery than following EVLA as assessed by the nurse at 6 weeks (–0.76, 95% CI –1.04 to –0.48; $p < 0.001$), but not at 6 months. Results were similar for participant-reported residual varicose veins at both time points.

Clinical, etiological, anatomical, pathological classification

Although the CEAP is not generally considered an appropriate measure of outcome, it is included for completeness, but not statistically analysed. All participants had a CEAP classification of C2 or above at recruitment. By 6 weeks, the proportion of participants with a classification lower than C2 was highest in the surgery group (76%), compared with only 47% for foam and 45% for EVLA (see *Table 55*). At 6 months, the proportion of participants with a classification better than C2 remained highest in the surgery group (74%), compared with 64% for EVLA and 59% for foam (see *Table 56*).

Pain

Immediately after treatment, the mean pain scores for those randomised to foam sclerotherapy, surgery and EVLA were 2.2 (SD 2.0), 2.4 (SD 2.6) and 3.5 (SD 2.2) respectively (see *Appendix 2*, *Table 107*). Patient-reported pain is significantly higher for EVLA than for either surgery or foam sclerotherapy. At 6 weeks, patients' recollection of pain during treatment was higher than that recorded after treatment for all three treatment modalities. Patients' recollection of the pain they experienced during foam sclerotherapy (mean VAS 3.0, SD 2.5) was significantly lower than for either surgery (mean VAS 4.1, SD 3.0) or EVLA (mean VAS 4.4, SD 2.8). Patients' recollection of pain during recovery was also significantly lower for foam sclerotherapy than for either surgery or EVLA. The pain experienced during recovery for surgery was significantly higher than that for EVLA.

Anatomical success

Success rates for truncal vein ablation at 6 weeks and 6 months are shown in *Tables 58* and *59*. The overall statistical analysis for the whole leg and the GSV only is shown in *Table 60*. The numbers undergoing treatment to the SSV alone or in combination with the GSV were small, and therefore these subgroups were not subjected to statistical analysis.

There were no differences in ablation success between surgery and EVLA. However, for all comparisons between EVLA and foam sclerotherapy, the OR was > 2, and the treatment effect on ablation rates is highly significant in favour of EVLA in each comparison ($p < 0.001$). At 6 months, the effect size in favour of EVLA over foam (GSV only) was 4.83 (95% CI 2.76 to 8.48, $p < 0.001$).

Complications

Procedural complications

The procedural complications noted at the time of the primary treatment are documented in *Table 61*. In the EVLA versus foam sclerotherapy comparison, the event rate for any procedural complication was significantly lower for EVLA (OR 0.17, 95% CI 0.05 to 0.60; $p = 0.006$). Similarly, in the surgery versus EVLA comparison, the event rate for any procedural complication was significantly higher for surgery (OR 5.41, 95% CI 1.73 to 16.89; $p = 0.004$). Five participants in the foam group (3%), five in the surgery group (3%) and none in the EVLA group experienced two procedural complications.

Later complications

Complications noted at the time of the 6-week and 6-month assessments are shown in *Tables 62* and *63*. Estimates of the effect of treatment on complications are summarised across both follow-up time points in *Table 64*, with ORs comparing surgery with EVLA, and EVLA with foam sclerotherapy.

TABLE 58 Truncal vein ablation at 6 weeks: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Anatomical success	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 weeks (*N*, *n*, %)	210	193	91.9	207	189	91.3	213	180	84.5
GSV involvement only									
Complete success (*N*, *n*, %)	153	127	83.0	152	96	63.2	143	122	85.3
Partial success (*N*, *n*, %)	153	23	15.0	152	36	23.7	143	15	10.5
without reflux (*N*, *n*, %)	153	13	8.5	152	29	19.1	143	9	6.3
with reflux (*N*, *n*, %)	153	10	6.5	152	7	4.6	143	6	4.2
Failure (*N*, *n*, %)	153	3	2.0	152	20	13.2	143	6	4.2
SSV involvement only									
Complete success (*N*, *n*, %)	12	6	50.0	11	5	45.5	12	3	25.0
Partial success (*N*, *n*, %)	12	4	33.3	11	4	36.4	12	7	58.3
without reflux (*N*, *n*, %)	12	4	33.3	11	4	36.4	12	5	41.7
with reflux (*N*, *n*, %)	12	0	0.0	11	0	0.0	12	2	16.7
Failure (*N*, *n*, %)	12	2	16.7	11	2	18.2	12	2	16.7
GSV and SSV involvement *GSV*									
Complete success (*N*, *n*, %)	9	4	44.4	15	9	60.0	11	9	81.8
Partial success (*N*, *n*, %)	9	2	22.2	15	3	20.0	11	0	0.0
without reflux (*N*, *n*, %)	9	1	11.1	15	1	6.7	11	0	0.0
with reflux (*N*, *n*, %)	9	1	11.1	15	1	6.7	11	0	0.0
Failure (*N*, *n*, %)	9	3	33.3	15	3	20.0	11	2	18.2
SSV									
Complete success (*N*, *n*, %)	6	1	16.7	16	2	12.5	11	1	9.1
Partial success (*N*, *n*, %)	6	1	16.7	16	3	18.8	11	3	27.3
without reflux (*N*, *n*, %)	6	1	16.7	16	2	12.5	11	1	9.1
with reflux (*N*, *n*, %)	6	0	0.0	16	0	0.0	11	2	18.2
Failure (*N*, *n*, %)	6	4	66.7	16	11	68.8	11	7	63.6
Overall treatment of study leg									
Complete success (*N*, *n*, %)	170	133	78.2	178	103	57.9	165	125	75.8
Partial success (*N*, *n*, %)	170	31	18.2	178	50	28.1	165	32	19.4
without reflux (*N*, *n*, %)	170	19	11.2	178	41	23.0	165	21	12.7
with reflux (*N*, *n*, %)	170	12	7.1	178	9	5.1	165	11	6.7
Failure (*N*, *n*, %)	170	6	3.5	178	25	14.0	165	8	4.8

TABLE 59 Truncal vein ablation at 6 months: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Anatomical success	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 months (*N*, *n*, %)	210	183	87.1	207	178	86.0	213	167	78.4
GSV involvement only									
Complete success (*N*, *n*, %)	141	116	82.3	132	67	50.8	127	101	79.5
Partial success (*N*, *n*, %)	141	16	11.3	132	31	23.5	127	16	12.6
without reflux (*N*, *n*, %)	141	13	9.2	132	22	16.7	127	3	2.4
with reflux (*N*, *n*, %)	141	3	2.1	132	9	6.8	127	13	10.2
Failure (*N*, *n*, %)	141	9	6.4	132	34	25.8	127	10	7.9
SSV involvement only									
Complete success (*N*, *n*, %)	9	6	66.7	11	4	36.4	11	3	27.3
Partial success (*N*, *n*, %)	9	3	33.3	11	2	18.2	11	3	27.3
without reflux (*N*, *n*, %)	9	2	22.2	11	1	9.1	11	3	27.3
with reflux (*N*, *n*, %)	9	1	11.1	11	1	9.1	11	0	0.0
Failure (*N*, *n*, %)	9	0	0.0	11	5	45.5	11	5	45.5
GSV and SSV involvement *GSV*									
Complete success (*N*, *n*, %)	10	6	60.0	14	5	35.7	9	7	77.8
Partial success (*N*, *n*, %)	10	2	20.0	14	4	28.6	9	1	11.1
without reflux (*N*, *n*, %)	10	2	20.0	14	3	21.4	9	0	0.0
with reflux (*N*, *n*, %)	10	0	0.0	14	1	7.1	9	1	11.1
Failure (*N*, *n*, %)	10	2	20.0	14	5	35.7	9	1	11.1
SSV									
Complete success (*N*, *n*, %)	7	2	28.6	13	2	15.4	9	1	11.1
Partial success (*N*, *n*, %)	7	2	28.6	13	1	7.7	9	0	0.0
without reflux (*N*, *n*, %)	7	1	14.3	13	1	7.7	9	0	0.0
with reflux (*N*, *n*, %)	7	1	14.3	13	0	0.0	9	0	0.0
Failure (*N*, *n*, %)	7	3	42.9	13	10	76.9	9	8	88.9
Overall treatment of study leg									
Complete success (*N*, *n*, %)	156	123	78.8	156	73	46.8	147	104	70.7
Partial success (*N*, *n*, %)	156	24	15.4	156	41	26.3	147	28	19.0
without reflux (*N*, *n*, %)	156	20	12.8	156	31	19.9	147	15	10.2
with reflux (*N*, *n*, %)	156	4	2.6	156	10	6.4	147	13	8.8
Failure (*N*, *n*, %)	156	9	5.8	156	42	26.9	147	15	10.2

TABLE 60 Estimates of the effect of treatment on truncal vein ablation: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam sclerotherapy		
Anatomical success	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	OR[a]	95% CI	*p*-value	OR[b]	95% CI	*p*-value
Complete success at 6 weeks (whole leg)	170	133	78.2	178	103	57.9	165	125	75.8						
Partial success without reflux at 6 weeks (whole leg)	170	19	11.2	178	41	23.0	165	21	12.7						
Partial success with reflux at 6 weeks (whole leg)	170	12	7.1	178	9	5.1	165	11	6.7						
Failure at 6 weeks (whole leg)	170	6	3.5	178	25	14.0	165	8	4.8	1.11	0.63 to 1.95	0.723	2.42	1.48 to 3.95	< 0.001
Complete success at 6 months (whole leg)	156	123	78.8	156	73	46.8	147	104	70.7						
Partial success without reflux at 6 months (whole leg)	156	20	12.8	156	31	19.9	147	15	10.2						
Partial success with reflux at 6 months (whole leg)	156	4	2.6	156	10	6.4	147	13	8.8						
Failure at 6 months (whole leg)	156	9	5.8	156	42	26.9	147	15	10.2	0.62	0.36 to 1.07	0.087	4.67	2.81 to 7.77	< 0.001
Complete success at 6 weeks (GSV)	153	127	83.0	152	96	63.2	143	122	85.3						
Partial success without reflux at 6 weeks (GSV)	153	13	8.5	152	29	19.1	143	9	6.3						
Partial success with reflux at 6 weeks (GSV)	153	10	6.5	152	7	4.6	143	6	4.2						
Failure at 6 weeks (GSV)	153	3	2.0	152	20	13.2	143	6	4.2	1.17	0.61 to 2.26	0.636	3.10	1.78 to 5.42	< 0.001
Complete success at 6 months (GSV)	141	116	82.3	132	67	50.8	127	101	79.5						
Partial success without reflux at 6 months (GSV)	141	13	9.2	132	22	16.7	127	3	2.4						
Partial success with reflux at 6 months (GSV)	141	3	2.1	132	9	6.8	127	13	10.2						
Failure at 6 months (GSV)	141	9	6.4	132	34	25.8	127	10	7.9	0.82	0.44 to 1.53	0.531	4.83	2.76 to 8.48	< 0.001

a An OR of > 1 favours surgery.
b An OR of > 1 favours EVLA.

TABLE 61 Procedural complications at time of primary treatment: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Procedural complication	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Treated (*n*)	205			197			195		
Any procedural complication[a] (*N*, *n*, %)	205	2	1.0	197	13	6.6	195	16	8.2
Wound haematoma (*N*, *n*, %)	205	0	0.0	197	1	0.5	195	1	0.5
Damage to major artery (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Damage to major vein (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Damage to major nerve (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Bleeding (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	2	1.0
Visual disturbance/blurred vision (*N*, *n*, %)	205	0	0.0	197	4	2.0	195	0	0.0
Extravasation of foam sclerotherapy (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	1	0.5
Allergic/anaphylactoid reaction (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Stroke (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Transient ischaemic attack (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Myocardial infarction (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Intra-arterial injection (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Epileptic fit (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Headache (*N*, *n*, %)	205	0	0.0	197	2	1.0	195	1	0.5
Transient confusion (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Panic attack (*N*, *n*, %)	205	0	0.0	197	1	0.5	195	0	0.0
Malaise (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Cough (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Chest tightness/heaviness (*N*, *n*, %)	205	0	0.0	197	1	0.5	195	0	0.0
Vasovagal (*N*, *n*, %)	205	0	0.0	197	3	1.5	195	1	0.5
Anaesthetic side effects (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	6	3.1
Sickness (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	4	2.1
Muscle pains (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	1	0.5
Sore throat (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	2	1.0
Damage to teeth, lip or tongue (*N*, *n*, %)	205	0	0.0	197	0	0.0	195	0	0.0
Other procedural complication (*N*, *n*, %)	205	2	1.0	197	6	3.0	195	6	3.1

a Some participants had more than one complication.

TABLE 62 Complications at 6 weeks: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Complication	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 weeks (*N*, *n*, %)	210	193	91.9	207	189	91.3	213	180	84.5
Any complication at 6 weeks (*N*, *n*, %)	193	103	53.4	189	149	78.8	180	118	65.6
Numbness (*N*, *n*, %)	193	22	11.4	189	10	5.3	180	30	16.7
Persistent bruising (*N*, *n*, %)	193	10	5.2	189	36	19.0	180	22	12.2
Persistent tenderness/discomfort (*N*, *n*, %)	193	41	21.2	189	76	40.2	180	57	31.7
Skin loss/ulceration (*N*, *n*, %)	193	0	0.0	189	2	1.1	180	1	0.6
Lumpiness (*N*, *n*, %)	193	36	18.7	189	104	55.0	180	51	28.3
Development of thread vein (*N*, *n*, %)	193	10	5.2	189	21	11.1	180	16	8.9
Skin staining (*N*, *n*, %)	193	18	9.3	189	66	34.9	180	11	6.1
Wound infection (*N*, *n*, %)	193	3	1.6	189	1	0.5	180	17	9.4
Backache (*N*, *n*, %)	193	4	2.1	189	5	2.6	180	7	3.9
Headache (*N*, *n*, %)	193	1	0.5	189	9	4.8	180	3	1.7
DVT (*N*, *n*, %)	193	0	0.0	189	2	1.1	180	0	0.0
Pulmonary embolus (*N*, *n*, %)	193	0	0.0	189	0	0.0	180	0	0.0
Stroke (*N*, *n*, %)	193	0	0.0	189	0	0.0	180	0	0.0
Myocardial infarction (*N*, *n*, %)	193	0	0.0	189	0	0.0	180	0	0.0
Loss of vision (*N*, *n*, %)	193	0	0.0	189	3	1.6	180	0	0.0
Damage to major artery (*N*, *n*, %)	193	0	0.0	189	0	0.0	180	0	0.0
Damage to major vein (*N*, *n*, %)	193	0	0.0	189	1	0.5	180	0	0.0
Damage to motor nerve (*N*, *n*, %)	193	0	0.0	189	0	0.0	180	0	0.0
Other complication (*N*, *n*, %)	193	10	5.2	189	14	7.4	180	17	9.4

TABLE 63 Complications at 6 months: comparisons of EVLA with foam sclerotherapy and surgery with EVLA

Complication	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Clinic assessment at 6 months (*N*, *n*, %)	210	183	87.2	207	178	86.0	213	167	78.4
Any complication at 6 months (*N*, *n*, %)	183	89	48.6	178	94	52.8	167	77	46.1
Numbness (*N*, *n*, %)	183	17	9.2	178	5	2.8	167	28	16.8
Persistent bruising (*N*, *n*, %)	183	25	13.6	178	26	14.6	167	34	20.4
Skin loss/ulceration (*N*, *n*, %)	183	1	0.6	178	1	0.6	167	0	0.0
Lumpiness (*N*, *n*, %)	183	25	13.6	178	46	25.8	167	10	6.0
Development of thread vein (*N*, *n*, %)	183	24	13.2	178	23	13.0	167	19	11.4
Skin staining (*N*, *n*, %)	183	32	17.4	178	55	30.8	167	13	7.8
DVT (*N*, *n*, %)	183	0	0.0	178	1	0.6	167	0	0.0
Pulmonary embolus (*N*, *n*, %)	183	0	0.0	178	0	0.0	167	0	0.0
Other (*N*, *n*, %)	183	11	6.0	178	8	4.4	167	10	6.0

TABLE 64 Estimates of the effect of treatment on complications: comparisons of EVLA with foam sclerotherapy and EVLA with surgery

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam sclerotherapy		
Complication type	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	OR[a]	95% CI	*p*-value	OR[b]	95% CI	*p*-value
Procedural complications at treatment	205	2	1.0	197	13	6.6	195	16	8.2	5.41	1.73 to 16.89	0.004	0.17	0.05 to 0.60	0.006
Any complication at 6 weeks	193	103	53.4	189	149	78.8	180	118	65.6	1.75	1.13 to 2.70	0.012	0.27	0.17 to 0.43	< 0.001
Any complication at 6 months	183	89	48.6	178	94	52.8	167	77	46.1	0.90	0.58 to 1.40	0.640	0.82	0.54 to 1.25	0.357
Numbness at 6 weeks	193	22	11.4	189	10	5.3	180	30	16.7	1.70	0.91 to 3.17	0.096	2.50	1.12 to 5.60	0.025
Numbness at 6 months	183	17	9.2	178	5	2.8	167	28	16.8	2.11	1.05 to 4.24	0.037	3.85	1.35 to 10.99	0.012
Persistent bruising at 6 weeks	193	10	5.2	189	36	19.0	180	22	12.2	2.86	1.26 to 6.51	0.012	0.17	0.07 to 0.38	< 0.001
Persistent bruising at 6 months	183	25	13.6	178	26	14.6	167	34	20.4	1.71	0.93 to 3.12	0.083	0.90	0.48 to 1.67	0.733
Persistent tenderness/discomfort at 6 weeks	193	41	21.2	189	76	40.2	180	57	31.7	1.90	1.16 to 3.11	0.011	0.36	0.22 to 0.58	< 0.001
Skin loss/ulceration at 6 weeks	193	0	0.0	189	2	1.1	180	1	0.6	N/C	N/C	N/C	N/C	N/C	N/C
Skin loss/ulceration at 6 months	183	1	0.6	178	1	0.6	167	0	0.0	N/C	N/C	N/C	1.50	0.06 to 40.60	0.810
Lumpiness at 6 weeks	193	36	18.7	189	104	55.0	180	51	28.3	1.84	1.11 to 3.05	0.018	0.15	0.09 to 0.25	< 0.001
Lumpiness at 6 months	183	25	13.6	178	46	25.8	167	10	6.0	0.43	0.19 to 0.97	0.041	0.38	0.21 to 0.68	0.001
Development of thread vein at 6 weeks	193	10	5.2	189	21	11.1	180	16	8.9	1.82	0.79 to 4.20	0.159	0.43	0.19 to 0.95	0.037
Development of thread vein at 6 months	183	24	13.2	178	23	13.0	167	19	11.4	0.80	0.41 to 1.57	0.520	1.03	0.55 to 1.96	0.917
Skin staining at 6 weeks	193	18	9.3	189	66	34.9	180	11	6.1	0.55	0.24 to 1.27	0.163	0.17	0.09 to 0.30	< 0.001
Skin staining at 6 months	183	32	17.4	178	55	30.8	167	13	7.8	0.38	0.19 to 0.78	0.009	0.41	0.24 to 0.70	0.001
Backache at 6 weeks	193	3	1.6	189	1	0.5	180	17	9.4	7.56	2.00 to 28.58	0.003	3.26	0.33 to 32.68	0.314
Headache at 6 weeks	193	4	2.1	189	5	2.6	180	7	3.9	1.61	0.43 to 6.04	0.477	0.71	0.18 to 2.83	0.623

N/C, not calculable.
a An OR of > 1 favours EVLA.
b An OR of > 1 favours foam sclerotherapy.

Comparison of endovenous laser ablation with foam

The event rates at 6 weeks for persistent bruising (OR 0.17, 95% CI 0.07 to 0.38; $p < 0.001$), persistent tenderness (OR 0.36, 95% CI 0.22 to 0.58; $p < 0.001$), lumpiness (OR 0.38, 95% CI 0.21 to 0.68; $p < 0.001$), skin staining (OR 0.41, 95% CI 0.24 to 0.70; $p < 0.001$), development of thread vein (OR 0.43, 95% CI 0.19 to 0.95; $p = 0.037$) and headache (OR 0.10, 95% CI 0.01 to 0.79; $p = 0.029$) were all significantly lower for EVLA than for foam. At 6 months, lumpiness (OR 0.38, 95% CI 0.21 to 0.68; $p = 0.001$) and skin staining (OR 0.41, 95% CI 0.24 to 0.70; $p = 0.001$) remained less frequent for EVLA than for foam. The event rate for cutaneous numbness (at both time points) is significantly higher for EVLA than for foam sclerotherapy (at 6 months, OR 3.85, 95% CI 1.35 to 10.99; $p = 0.012$).

Comparison of surgery with endovenous laser ablation

The rates for persistent bruising (OR 2.86, 95% CI 1.26 to 6.51; $p = 0.012$), persistent tenderness (OR 1.90, 95% CI 1.16 to 3.11; $p = 0.011$) and lumpiness (OR 1.84, 95% CI 1.11 to 3.05; $p = 0.018$) at 6 weeks were all significantly higher for surgery than for EVLA. At 6 months, cutaneous numbness (OR 2.11, 95% CI 1.05 to 4.24; $p = 0.037$), lumpiness (OR 0.43, 95% CI 0.19 to 0.97; $p = 0.041$) and skin staining (OR 0.38, 95% CI 0.19 to 0.78; $p = 0.009$) occurred more frequently for surgery than for EVLA.

Serious adverse events

Table 65 gives brief details of the seven SAEs reported in participants randomised to EVLA. One of these (pain in the contralateral leg treated at the same time as the study leg) was assessed as related to treatment. A further SAE (fall resulting in rib fracture) was assessed as possibly related to treatment because the participant was still wearing compression stockings at the time of the fall and was thought to be slightly incapacitated because of these. The other five SAEs were not related to treatment. Details of the SAEs in those randomised to surgery and foam sclerotherapy are given in *Chapter 5* (see *Table 39*).

Process evaluation: Illness Perception Questionnaire – Revised

Detailed descriptive results of the IPQ-R are given in *Appendix 2* (see *Table 109*). Within each randomised group, the mean identity scores and the percentage of symptoms correctly identified as being related to varicose veins at baseline (recruitment) and after the participant had been informed of his or her randomisation were similar. By 6 months, both measures of illness identity had fallen.

For all other measures of illness perception, there is very little difference between scores at baseline and post randomisation. For most of the domains, there were decreases in the mean scores between baseline and 6 months in all groups. The exceptions to this were for personal control and illness coherence, where the mean scores increased slightly in all groups. For all of these domains, the differences between surgery and EVLA, and EVLA and foam sclerotherapy were marginal.

TABLE 65 Serious adverse events detected up to the time of the 6-months follow-up: EVLA

Randomised	Treatment prior to SAE	Description of event	Related to treatment?	Expected?
EVLA	EVLA	Pain in contralateral leg (treated at same time as study leg); possibly related to osteoporosis	Yes	No
EVLA	EVLA	Fall; rib fracture	Possible	No
EVLA	EVLA	Surgery for fractured shoulder	No	No
EVLA	EVLA	Pain in thigh and groin; cellulitis	No	No
EVLA	EVLA	Injury at work – trauma to hand	No	No
EVLA	EVLA	Episode of palpitation	No	No
EVLA	No treatment	Migraine	No	No

Chapter 7 Clinical effectiveness

Primary outcome: Aberdeen Varicose Vein Questionnaire score

Main findings

This is the first RCT involving foam sclerotherapy to evaluate and report disease-specific QoL as a primary outcome measure. In all groups, disease-specific AVVQ scores improved over time (i.e. scores reduced). The health gain obtained in the AVVQ was lower in patients undergoing foam sclerotherapy than in those receiving surgery at 6 weeks ($p = 0.006$) and at 6 months ($p = 0.0002$). This equated to a difference in scores of 2.26 between the groups at 6 weeks and 1.74 at 6 months, which is likely to be of clinical significance. The health gains in the AVVQ in patients undergoing foam sclerotherapy and EVLA were similar, as were those in the EVLA and surgery comparison.

Comparison with published randomised controlled trials/patient-reported outcome measures

It is of note that the baseline AVVQ scores in the CLASS study (17.91) are similar to those observed in the PROMs for the NHS in England (18.53 in 2010). At 6 weeks there was a more than 5-point fall (improvement) in the AVVQ score compared with baseline in all treatment groups. In the surgery arm, by 6 months the AVVQ score more than halved compared with baseline (a fall of 10.4 points). Similarly, scores in the foam sclerotherapy and EVLA groups almost halved (falls of 8.5 and 9.9 points respectively). The reduction in AVVQ score (measured at least 3 months post treatment) observed in PROMs data for NHS England (7.9 points)[44] sits within the values observed in CLASS at 6 weeks and 6 months. Thus, the CLASS results appear generalisable to that obtained in the NHS in England.

The 2007 study by Rasmussen *et al.*[36] reported similar baseline scores to those obtained in the CLASS study but had slightly greater health gains (a fall of 10.8 in the surgery group and 11.5 in the EVLA group at 6 months post treatment). Christenson *et al.*[34] reported higher baseline scores than both Rasmussen *et al.* (2007)[36] and ourselves, and, by 12 months, a slightly greater improvement in patients undergoing EVLA or surgery.

We have shown, as have previous RCTs, that all three treatment modalities are associated with a health gain (reduction) in the AVVQ score.[15,29,32,34,36,37,50] Four of these studies assessed the AVVQ at 4–6 weeks.[29,36,37,50] In contrast to our findings, the previous study which compared foam with surgery and EVLA with foam assessed AVVQ at similar time points to CLASS and found no differences between AVVQ scores.[29] In common with CLASS, the studies that have assessed AVVQ at later time points have also found no difference between EVLA and surgery.[15,29,34,37,50] It is worth noting that the AVVQ was not the primary outcome measure in any of these previous studies; thus, they are unlikely to have been adequately powered to detect a difference.

With the exception of one site, we did not perform simultaneous phlebectomies in patients undergoing EVLA. This site (Hull) had previously performed a RCT which showed significant improvements in disease-specific QoL (assessed by AVVQ) in patients undergoing simultaneous compared with delayed phlebectomies following EVLA at 6 weeks and 3 months.[73]

European Quality of Life-5 Dimensions

Main findings

In all treatment groups, a health gain (increase in EQ-5D score from baseline) was observed at the 6-weeks and 6-months time points. Most of the health gain was achieved between baseline and 6 weeks. There was a health gain at 6 weeks in patients randomised to EVLA compared with those randomised to foam

for the EQ-5D ($p = 0.004$). There were no differences at 6 months. There were no differences in surgery versus EVLA or surgery versus foam sclerotherapy. At 6 months, there were no significant differences in the comparisons of foam sclerotherapy with surgery, EVLA with surgery or EVLA with foam sclerotherapy.

European Quality of Life-5 Dimensions visual analogue scale

At 6 weeks, the EQ-5D VAS score increased in patients randomised to surgery or EVLA. There was no change in those randomised to foam sclerotherapy. However, by 6 months there was a rise in all treatment groups (rise of 2.0–4.5). There were no statistical differences between groups at 6 weeks or 6 months.

Comparison with published randomised controlled trials/patient-reported outcome measures

The CLASS baseline EQ-5D scores (0.79) were similar to the baseline scores in the PROMs (0.77) for NHS England.[44] The health gain observed in CLASS (0.10–0.11) was similar to that seen in the PROMs (0.091). The EQ-5D VAS baseline score observed in CLASS (80.0–80.6) was similar to that observed in the PROMs (79.25). However, unlike the improvement seen in our study, in the PROMs the EQ-5D VAS showed no real change when assessed at least 3 months post treatment (fall of –0.098).

Similar to our findings, previous studies have shown an increase in EQ-5D scores at time points from 6 weeks to 2 years. In the study by Shadid,[33] the mean change in the EQ-5D score from baseline to 2 years (a gain of 0.064 for foam sclerotherapy and 0.061 for surgery) was slightly lower than that obtained in the CLASS study at 6 months (a gain of approximately 0.1). In the study by Carradice *et al.*,[73] by 6 weeks, mean scores for both surgery and EVLA groups had increased to 1.0 (substantially higher than the mean scores observed in CLASS). The study by Samuel *et al.*,[37] which involved only patients with SSV involvement, also showed an increase in EQ-5D scores (of approximately 0.12 at 12 months for both surgery and EVLA groups), with the mean scores for surgery reaching 1.0 by 6 weeks. Unlike previous studies, CLASS showed an early improvement in the EQ-5D in patients receiving EVLA compared with foam and surgery compared with foam.

Short Form questionnaire-36 items

Main findings

The SF-36 physical component score was higher in all three treatment groups at 6 weeks than at baseline. Further increases in scores were observed at the 6-months time point.

There were no statistical differences between foam and surgery for the overall physical and mental component scores or domains of the SF-36. However, the general health domain showed a significant improvement for surgery compared with foam at 6 weeks ($p < 0.005$).

Patients randomised to EVLA had similar health gains to those who underwent foam sclerotherapy in the overall SF-36 physical component and individual physical domains at 6 weeks and 6 months. This difference was not apparent at 6-months follow-up. Similar improvements in the overall SF-36 mental component score and domains were shown for both EVLA and foam sclerotherapy.

At 6 weeks, patients randomised to EVLA had a greater health gain than those who underwent surgery in the SF-36 individual domains of vitality, social functioning and role emotional ($p < 0.005$). The overall physical scores were similar but the role physical and bodily pain domains were significantly improved for EVLA compared with surgery at 6 weeks ($p < 0.005$).

Comparison with published randomised controlled trials/patient-reported outcome measures

Short Form questionnaire-36 items scores were not collected in PROMs. One previous RCT involving a comparison of EVLA and surgery used the SF-36 as a primary outcome measure.[50] This study, by Carradice *et al.*, showed an initial reduction in some component scores at 1 week, but by 6 weeks significant improvements were detected in five of the eight domains (physical function, role physical, bodily pain, general health, vitality). Although the increases are in tune with those seen in CLASS, Carradice *et al.*[50] found no differences between groups. In contrast, in the CLASS trial there were significantly greater improvements for EVLA than for surgery in six of the domains ($p < 0.05$) at 6 weeks, with the improvement in the mental health domain remaining significant at 6 weeks. Four further RCTs which compared EVLA with surgery have also assessed generic QoL using the SF-36.[29,34,36,37] It is of note that all these studies assessed outcome early (1 month or 6 weeks), as was done in the CLASS study.[29,36,37,50] All reported improvements in some or all domains following treatment, but, unlike the CLASS trial, which showed a greater gain for EVLA than for surgery, no differences were detected.[29,34,36,37] One of these studies also included a comparison of EVLA and foam sclerotherapy, and found no difference between the treatment arms.[29] In contrast, in the CLASS trial, early benefits in favour of EVLA over foam sclerotherapy were found in two of the domains ($p < 0.05$), with a significant improvement in the mental health domain for EVLA at 6 months. The CLASS trial also showed significant benefits of surgery over foam sclerotherapy in two domains.

Venous Clinical Severity Score

Main findings

Up to 6 months, the VCSS improved in all three treatment groups. At 6 weeks, the improvement in the VCSS (reduction in score) was significantly greater in patients undergoing surgery than in those receiving foam sclerotherapy (0.52-point difference in scores, $p = 0.002$). A further, smaller reduction was observed in all groups at the 6-months follow-up, but at this stage there were no statistical differences between groups.

Comparison with published randomised controlled trials

The mean baseline score in CLASS (5.0) was within the range of baseline VCSS scores reported in previous RCTs (2.4–7).[15,29,32,34,36,37,50] All studies noted a reduction in VCSS at 3 months or longer.

In the CLASS study, the VCSS at 6 months was slightly higher (1.6) in the foam sclerotherapy group (i.e. that group had the most residual vein-related symptoms) than in the EVLA and surgery groups (1.4 and 1.3 respectively), but the differences were not statistically significant. The magnitude of the fall (3.1–3.7) was similar to those reported in some RCTs[15,32] but greater than that observed by Rasmussen's group,[36,49] which reported lower baseline scores (2.4–2.8 and 5 respectively) than in CLASS.

The 6-months score was slightly higher than those of some studies (which had scores of 0–1), but many of these studies had lower baseline scores at the outset.[15,29,34,36,50] One previous single-site RCT[73] found that the improvement in VCSS was significantly better at both 6 weeks and 3 months in patients who had EVLA and simultaneous phlebectomies than in those who underwent delayed phlebectomies. Although performing EVLA and simultaneous phlebectomies in the CLASS trial might therefore have further improved VCSS at 6 weeks, patients were given the option of foam sclerotherapy at 6 weeks, and thus it is unlikely that performing simultaneous phlebectomies would have influenced the 6-months VCSS score.

Residual varicose veins: visual analogue scale

Main findings

The VAS scores reported by the nurses were consistently lower (representing fewer varicose veins), at all time points and for all three treatment modalities, than the VAS scores reported by the patients. At 6 weeks, the patient-reported VAS scores were lower (fewer varicose veins) in the surgery group than in the foam sclerotherapy group (0.99-point difference, $p < 0.001$). Similarly, at 6 months the patient-reported VAS scores were lower (fewer varicose veins) in the surgery group than in the foam sclerotherapy group (0.95-point difference, $p < 0.001$). There were no differences between the EVLA and foam sclerotherapy groups at 6 weeks, but at 6 months the score was lower (fewer varicose veins) in the EVLA group (0.54-point difference, $p = 0.005$).

A similar pattern was seen for the nurse-reported VAS scores, with the exception that no differences were noted between the EVLA and foam sclerotherapy groups at 6-weeks and 6-months follow-up. The consistently lower scores recorded by the nurses compared with the patients may be due to the nurses' prior exposure to patients with more complex and extensive varicose veins, which could have given them a higher 'threshold' in their judgements about the visual appearance of leg veins.

The presence of an increased number of residual varicosities in the patients undergoing foam at 6-weeks follow-up is explained by the fact that patients had not completed their treatment for calf varicosities by this stage (with the exception of patients at one centre which performed concomitant phlebectomies with EVLA).

Comparison with published randomised controlled trials

The presence of residual varicose veins was not reported in any of the previous RCTs. However, patient-reported cosmesis was recorded in the study by Darwood[15] and showed no differences between patients undergoing EVLA and those receiving surgery. The findings in CLASS are an interesting and potentially important observation, because they suggest that surgeons involved in those trials did not see residual veins as an issue. By contrast, the expectation of other surgeons (and patients) is that treatment will get rid of all varicose veins in the treated leg. These contrasting aims and expectations are fundamental in judging the 'success' of any treatment for varicose veins and they are important to consider in interpreting the conclusions of any study.

Visual analogue scale score and further treatment of residual varicosities with foam sclerotherapy

The patient-reported VAS scores at 6 weeks for the foam sclerotherapy, EVLA and surgery groups were 2.6, 2.2 and 1.7 respectively. The decision to proceed with further treatment of residual varicosities at the 6-weeks stage in the foam sclerotherapy and EVLA groups was patient led. In the CLASS study, excluding the patients who underwent concurrent phlebectomies in Hull, 31% of the EVLA patients underwent foam sclerotherapy to their residual varicosities, including 2% who underwent a second foam sclerotherapy treatment. In the foam sclerotherapy group, 31% had treatment to their calf varicosities at their primary treatment session and a further 7% received further foam sclerotherapy to their residual varicosities. The presence of complications relating to treatment at the 6-weeks time point (see *Complications*) may have influenced the patients' decision regarding whether or not they should proceed with further foam sclerotherapy treatment to residual varicosities.

Comparison with published randomised controlled trials

In the six studies[14,29–33] which involved foam sclerotherapy, only three[14,30,33] administered delayed foam sclerotherapy for residual tributaries (see *Chapter 2*). Similar to our study, in the Varisolve® study[14] 8% of patients had a further treatment session. In contrast, in the study by Figueiredo,[30] all but 3 of the 27 patients underwent one or more further treatment session. In the remaining study[33] which offered delayed phlebectomies or foam sclerotherapy, the number of patients who underwent further treatment is not stated.

In studies involving EVLA, only two used foam sclerotherapy to treat residual tributaries at a later stage.[15,40] In the Darwood study,[15] this was performed in 36% of patients, which is a similar rate to the CLASS trial. Details regarding the number of patients who had delayed foam sclerotherapy in the other study are not published.[40] The remainder of the studies treated the calf varicosities at the same time as the main truncal veins. Given that few patients randomised to EVLA underwent delayed treatment of residual varicosities in the CLASS trial, a policy of concomitant treatment of calf varicosities and the main truncal vein may result in a considerable number of patients receiving unnecessary treatment to calf varicosities.

Duplex-detected ablation of the main truncal vein (great saphenous vein/small saphenous vein)

The joint statement from the Venous Forum and the Society of Interventional Radiology[62] recommended reporting standards for endovenous ablation in the treatment of venous insufficiency. Anatomical success was defined as successful ablation *of the entire treated segment* of the target vein (absent flow or disappearance of the vein on duplex ultrasound). This guidance was used in the CLASS study; the duplex findings were reported by independent technicians at set anatomical locations.

In accordance with the above statement, we defined complete anatomical success for the GSV as complete occlusion at the groin (within 3 cm of the common femoral vein), complete occlusion at mid-thigh and either an occluded or a patent but non-refluxing GSV above the knee. It is of note that 90% of patients in CLASS who underwent GSV treatment had reflux above the knee only at baseline. The justification for not including the recorded 'within 1 cm of the common femoral vein' site in our definition was that, with the exception of one centre, this section was not treated. For foam sclerotherapy, our practice was to apply manual compression at the junction to reduce passage of foam into the common femoral vein.

Main findings

We have presented the anatomical success rates achieved for the truncal veins of the patient's study leg and for those patients undergoing treatment to the GSV alone. Higher rates of ablation success were obtained for patients undergoing treatment of the GSV alone than for those undergoing treatment of the SSV alone, or the GSV and SSV combined. There were no statistically significant differences in anatomical success between surgery and laser at either the 6-weeks or the 6-months time point, but both were superior to foam at these time points ($p < 0.001$).

The anatomical success achieved with foam sclerotherapy did not improve between the 6-weeks and 6-months follow-ups. The protocol allowed for further foam sclerotherapy to be given at the surgeon's discretion to any patent truncal vein at or after the 6-weeks follow-up, but in practice this was only performed in 12 participants randomised to foam sclerotherapy. There may be a number of reasons why further foam sclerotherapy to the truncal vein was not administered. For instance, it is often difficult to treat segmental isolated sections of the GSV, and the need to treat non-refluxing patent sections of the GSV is also questionable. It should be noted that of those patients who were considered to have had a partial anatomical success following foam sclerotherapy, only 4% had GSV reflux present at 6 weeks.

The definition of anatomical success for the SSV disadvantaged surgery, as the vein was not stripped in the majority of centres in the CLASS study (only 15 patients had stripping of the SSV performed). The number of patients undergoing SSV treatment was low ($n = 56$), and therefore we have not performed a statistical analysis of anatomical success within this group. The proportion of patients who underwent combined GSV and SSV treatment was also very low and, similarly, was not subjected to formal statistical analysis. Overall, the results for the SSV appear inferior to those obtained for the GSV, but the ablation success rates at 6 months appeared to be higher for EVLA than for either surgery or foam sclerotherapy.

In CLASS, the impact of anatomical success on symptoms, residual varicose veins and QoL following treatment is unclear. Despite the significant reduction in anatomical success following foam sclerotherapy, the VCSS, presence of residual varicose veins (nurse assessed) and generic QoL were similar to those achieved following EVLA and surgery. Thus, although anatomical success rates may be important in terms of future clinical recurrences, they have little effect (if any) on symptoms or QoL.

Comparison with published randomised controlled trials

The anatomical success rates for the GSV observed at 6 months in CLASS were lower than those reported in most previous RCTs for all three treatment modalities. This difference is most notable for the complete anatomical success achieved in CLASS for foam sclerotherapy (51% in the three-arm centres included in stratum A; 43% in the two-arm centres in stratum B), when compared against success rates of between 72% and 94% in previous studies where success was assessed at between 3 and 12 months.[14,29,30,33] In the study by Lattimer *et al.*,[32] success at 3 months was reported for above and below the knee separately (69% and 44% respectively). The lower anatomical success rates for foam sclerotherapy occurred despite the majority of procedures being performed by consultant surgeons in CLASS, so inexperience is unlikely to be a factor. The reasons for the lower anatomical success rate achieved in stratum B compared with stratum A are likely to be multifactorial and reflect NHS practice across the UK. For surgery and EVLA, the difference between CLASS and previous studies is less marked.

At 6 months, 82% of those undergoing EVLA in CLASS had complete anatomical success; this is slightly lower than the range reported in most previous RCTs (84–99%).[15,29,34–36] Again, in the study by Lattimer,[32] lower success rates were observed (74% above knee and 15% below knee).

Although lower than for many previous RCTs, the anatomical success rate of 78% at 6 months following surgery does lie within the range of success rates reported in previous RCTs (72–100%).[14,15,29,30,33–37]

There are a number of possible reasons for the lower anatomical success rates observed in CLASS. Firstly, in the CLASS study anatomical success in all but one centre was reported by independent, accredited vascular technicians. This was not the case in previous studies, which could have resulted in a bias towards reporting favourable outcomes in those studies. Secondly, the definitions of anatomical success (and/or failure) vary considerably between studies and many were less stringent in terms of complying with the joint statement of the Venous Forum, particularly for studies involving foam.[62] With the exception of one previous RCT,[32] outcomes were reported as success or failure, yet the definitions of failure varied considerably (*Table 66*).

This variation means that the duplex findings said to represent success in one study (for example the Rasmussen study[29]) might be considered only a partial success (or even a failure) in the CLASS study. Indeed, if the complete and partial non-refluxing success rates in the CLASS trial were combined, these would give ablation rates comparable with those of the Rasmussen paper for EVLA (91.4%). However, rates still remain lower for surgery (82%) and foam sclerotherapy (67%). Nevertheless, the results achieved with foam are comparable with the 69% rate obtained in the study by Latimer *et al.*[32] and the 68% rate obtained by surgeons in the study by Wright *et al.*[14] Thirdly, it is of note that most previous RCTs were conducted in single centres by enthusiasts in the field. This raises the possibility that these surgeons achieved better outcomes than the generality of vascular surgeons and their trainees and/or that a bias resulted towards reporting favourable outcomes. In CLASS, consultants performed 59%, 73% and 77% of surgical procedures, EVLA and foam sclerotherapy respectively.

The findings of CLASS were in accord with those in the Rasmussen[29] and Biemans[31] studies which showed significantly better technical success rates for surgery than for foam sclerotherapy. Only one study found an advantage of foam sclerotherapy over surgery.[30]

In two[29,31] of the three RCTs[29,31,32] which compared foam sclerotherapy with EVLA, technical success was significantly higher in patients randomised to EVLA, which is similar to our findings in CLASS.

TABLE 66 Definition of anatomical outcomes in previous RCTs

Study	Anatomical outcome
Rasmussen 2011[29]	Success: closed or absent GSV with lack of flow Failure: open part of the treated GSV above the knee of > 10 cm in length
Rasmussen 2007[36]	Success: closed or absent GSV or closed GSV with lack of flow Failure: open part of the treated vein of > 5 cm in length
Carradice 2009[35]	Success: absent GSV in thigh; closed or absent GSV with absent flow in treated segment of thigh
Darwood 2008[15]	Success: abolition of reflux in the treated GSV segment
Christenson 2010[34]	Success: absent GSV, closed or absent GSV with no flow including absent junctional reflux
Wright 2007[14]	Success: closed or absent GSV including absent junctional reflux
Samuel 2013[37]	Success: abolition of SSV reflux
Lattimer 2013[32]	Different criteria for success, including: • occlusion (any length) with or without reflux • occlusion (with or without reflux) or competency (patent and compressible with absence of flow or presence of antegrade flow) • occlusion (with or without reflux)
Rass 2011[38]	Success: closed or absent GSV
Figueiredo 2009[30]	Foam sclerotherapy: (1) total occlusion, (2) partial recanalisation without reflux, (3) partial recanalisation with reflux, (4) total recanalisation [success is defined as (1) and (2)] Surgery: failure defined as presence of reflux or residual varicose veins
Biemans 2013[31]	EVLA and foam sclerotherapy: success defined as complete obliteration, without flow or reflux, of the GSV at the level of the mid-thigh Surgery: success defined as absence of GSV in saphenous compartment at mid-thigh level

Of the 10 studies that compared EVLA and surgery, the majority (six) reported no significant difference in technical success rates and were thus similar to the CLASS study.[29,31,34,36,39,40] In contrast, three studies reported a significantly higher technical success rate for EVLA[15,35,37] and one for surgery.[38]

Complications

Serious adverse events

Ten SAEs were reported in patients randomised to foam sclerotherapy, but only three of these were related to the treatment. All three were non-occlusive DVT. There were seven SAEs in patients randomised to EVLA, of which one was related to the procedure (prolonged discomfort in non-study leg treated simultaneously). In patients randomised to surgery, 4 of 10 reported SAEs were secondary to the operation (two infections, one haematoma and one peroneal nerve injury).

Procedural complications

These were more common in patients randomised to surgery and foam sclerotherapy than in those undergoing EVLA (surgery 7.1–8.2%, foam 6.2–6.6%, EVLA 1%; $p < 0.001$). Patients appeared to report less pain immediately following the treatment with foam sclerotherapy than after EVLA or surgery. Patients' later recollection of pain experienced at the time of treatment and during recovery was also lower for foam sclerotherapy.

The majority of the complications in the surgery group were anaesthetic related. Following foam sclerotherapy, visual disturbance was experienced by 1.5% of patients, but there were no reports of more serious complications such as stroke, despite historical concerns about the possible effect of foam entering the systemic circulation.

Later complications

At 6 weeks, complications were increased in patients randomised to foam compared with EVLA or surgery ($p < 0.05$) and in patients undergoing surgery compared with EVLA. At 6 weeks, skin staining, bruising, persistent tenderness/discomfort, development of thread veins and lumpiness were statistically more common in the patients randomised to foam sclerotherapy than in those who had surgery or EVLA. Cutaneous numbness was statistically more common in patients randomised to surgery (17.6%) or EVLA (12%) than in those undergoing foam sclerotherapy (4.4%).

At 6 months, the total complication rate was higher for foam than for surgery ($p < 0.05$). There were no differences at this time point between EVLA and foam sclerotherapy. At 6 months, the proportion of patients who had skin staining had doubled in the EVLA group, presumably because of subsequent foam sclerotherapy for residual varicosities. Lumpiness was more common in the EVLA and foam sclerotherapy groups than in those undergoing surgery. Persistent bruising and cutaneous numbness were more common in those patients randomised to surgery.

Persistent lumpiness may have accounted for the increase in patient- and nurse-reported residual veins (VAS) at 6 months, because any lumps on the legs can mimic varicose veins. The presence of lumpiness and skin staining after foam sclerotherapy may have made some patients less willing to undergo further treatment sessions. Lumpiness, skin staining and tenderness are so common after foam sclerotherapy that it would be reasonable to consider them as expected sequelae rather than 'complications'. It is certainly important that patients be warned that they will occur and that they may take a long time to resolve.

Comparison with published randomised controlled trials

The type and frequency of complications observed in CLASS were similar to those documented in previous RCTs. It is worthy of note that no DVTs were identified in the patients undergoing EVLA or surgery, but three occurred in patients undergoing foam sclerotherapy. The role of DVT prophylaxis with low-molecular-weight heparin in conjunction with foam sclerotherapy has not been established and only 5% of patients received this in CLASS. This is similar to the proportion who received it in the EVLA group (7%) but much lower than that in the surgery group (48%).

Illness perceptions

No previous RCTs have assessed illness perception. We assessed illness perceptions at two time points before treatment (at recruitment, and after the participant was informed of his or her randomisation) and at 6 months. The reason for assessing illness perceptions at two time points before treatment was to assess whether or not the illness perceptions of participants in any of the trial arms changed after they were notified of the treatment to which they had been randomised. If there had been differences in illness perceptions between either the trial arms or the two time points, this may have influenced recovery behaviours or participants' self-reporting of QoL post treatment. In particular, if there had been differences between randomised groups, this may have introduced bias into the study. However, illness perceptions between baseline and after the participants were informed of their randomisation were very similar, as were illness perceptions between randomised groups at both time points. This suggests that revealing the randomised treatment allocation to participants (as was necessary in a trial where blinding of participants was not possible) did not introduce bias in terms of their reported illness perceptions. This increases our confidence in the QoL outcomes at 6 weeks and 6 months.

Illness identity was reduced by 6 months in all groups, and this probably reflects a reduced number of symptoms experienced by the participants after treatment. In those patients randomised to EVLA or foam, the percentage of symptoms correctly identified as being related to varicose veins increased; in part this is again likely to reflect a reduced number of symptoms, but may also reflect increased understanding of those symptoms likely to be related to varicose veins.

For all three treatments, the timeline domain relating to acute or chronic condition decreased. This means that participants' views that varicose veins last a long time had changed, and that they believed the timeline was shorter. Scores for the treatment control domain also reduced by 6 months. Both of these observations suggest that participants recognised some effectiveness of their treatment.

The consequences domain had reduced by 6 months in all groups, indicating that participants felt that the consequences of having varicose veins were less severe than they had previously reported. Emotional representations also reduced by 6 months in all groups. The findings across these domains are likely to reflect the effect of treatment on the varicose veins. As previously shown, treatment improves QoL and clinical outcomes; this analysis shows that there is also a benefit of treatment to patients at an emotional level.

Chapter 8 Behavioural recovery after treatment for varicose veins

As described in *Chapter 3*, one of the secondary outcomes in CLASS was 'behavioural recovery', or return to normal activities, which is regarded as an aspect of clinical success. One of the studies published prior to CLASS being funded showed that return to normal activities was considerably shorter following foam sclerotherapy than after surgery.[14] However, in that study it is not clear if 'normal activities' were defined or described for participants. We hypothesised that after any particular treatment there may be earlier return to some activities but later return to others, when compared against other treatments. With this in mind, we searched for suitable instruments to assess different types of normal activity, but found none. We therefore developed an instrument, BRAVVO, to assess distinct aspects of normal activities. In this chapter, we describe the theoretical underpinning of the development of the instrument and the development process. We also present the trial results generated by the BRAVVO instrument.

Theoretical background

The development and content validation of the BRAVVO questionnaire was informed by the World Health Organization (WHO) International Classification of Disability and Function (ICF) model.[74] The ICF model proposes that 'impairment' (defined as problems in body function or structure) is only one component of health outcome, the aspect that is based on a medical model of health or disease. The other two components of the ICF model are 'activity' (tasks or actions that an individual is capable of doing in an idealised situation) and 'participation' (what the individual actually does in an everyday, 'real world' situation). Variation in activity and participation is not fully explained by impairment, and so these constructs are important additional indicators of health outcome. It has been proposed that activity and participation can be defined in behavioural terms;[75] thus, the assessment of activity and participation is potentially a useful indicator of health outcome following treatment for varicose veins, over and above the AVVQ (which is primarily a measure of impairment). The BRAVVO questionnaire was therefore developed as an instrument to assess the activity and participation components of the ICF model following treatment for varicose veins. Being able to return to these activity or participation behaviours following treatment suggests recovery in terms of these behaviours, and we have termed this 'behavioural recovery'.

Development of an instrument to assess return to normal activities (behavioural recovery)

Methods

We developed a questionnaire to assess behavioural recovery. An interview study was carried out to identify normal activities and 'milestone' behaviours to incorporate into the questionnaire.

Eligibility criteria

Patients who had recently undergone treatment for their varicose veins at Aberdeen Royal Infirmary (ARI) were eligible to participate in the interview study if they

- had undergone recent treatment for their varicose veins (surgery, EVLA or foam sclerotherapy within the previous 6–12 weeks)
- were 18 years of age or older
- could speak English and were able to participate in the interview
- consented to participate.

Recruitment

Potential participants were identified from treatment lists at ARI and purposively sampled to provide a balance of those who received each of the three forms of treatment (surgery, EVLA or foam sclerotherapy). In addition to sampling from the three treatment options, diversity sampling was used in an attempt to gain a mix with regard to sex, age and rural–urban location.

Potential participants were invited, by letter sent from a vascular surgeon based at ARI, to take part in the interview study. They were each provided with a study information leaflet, invited to make contact with the research team for clarification of queries or further information, and asked to return a reply-paid slip or make contact by telephone if they wished to participate in the study. Study paperwork is included in *Appendix 1*.

Patients who wished to participate in the study were then contacted by telephone to arrange an interview. Those who wished to participate but were unable to travel to the hospital campus were asked if they would be prepared to participate in an interview in their home. Participants were compensated for costs incurred in taking part (e.g. travel, parking, child care).

Interview schedule

A topic guide (see *Appendix 3*) was prepared to assist the interviewer in eliciting behavioural milestones that patients regarded as significant. For the first 11 interviews, milestones were explained as 'Things that you looked forward to doing for the first time, were worried about doing for the first time, or felt pleased that you had achieved when you did them for the first time, after your treatment for varicose veins.' Based on the reports of several participants that there was nothing in particular that they looked forward to, this was altered to 'What couldn't you do straight after your treatment?'

Interviews

At the interview, participants were asked to sign a consent form indicating their agreement to participate in the study and to be audio-taped. An experienced interviewer (DB) used the topic guide to ask open questions (followed by appropriate prompts as required) to identify the actions that patients regarded as 'milestones' during their recovery. Interviews were audio-taped and transcribed verbatim. The interviewer then anonymised the transcripts.

Analysis of interview data

Interview transcripts ($n = 17$) were content analysed in four stages in order to identify appropriate items to include in a questionnaire.

First, one researcher (DB) identified, by highlighting, each utterance (or unit of text) that referred to a behaviour ('behavioural description'). To validate this first step, a second researcher (JF) read two transcripts to identify omissions in highlighting. No omissions were identified.

Second, each unit of highlighted text was pasted into a coding table and a 'label' (unique descriptor) was generated to describe each of the behaviours. Two researchers (DB, JF) independently coded five transcripts, discussing disagreements until consensus about these labels was reached. The 12 other transcripts were coded by a single researcher (DB) using this set of labels as a guide, and additional labels proposed when required.

In the third step of the analysis, using data from all the interviews, two researchers (DB, SC) independently allocated the units of text identified in the first step to one of the labels identified in the second step. A frequency table (representing the number of times a particular behaviour had been mentioned across all the interviews) was generated. Intercoder agreement was assessed and any additional labels identified by either researcher were included in the frequency table. The relevance or importance of each behaviour was assumed to be reflected by the frequency data.[76]

Finally, in the fourth stage of the content analysis, three researchers (DB, JF, SC) discussed the frequency table and identified (i) the most frequently mentioned behaviours (that merited a questionnaire item) and (ii) less frequently mentioned behaviours that could be grouped together to generate a questionnaire item which would encapsulate these behaviours. The behaviours identified using these methods were used to generate items for the BRAVVO questionnaire.

International Classification of Disability and Function classification of behaviours included in the Behavioural Recovery After treatment for Varicose Veins questionnaire

Distinguishing between impairment and the other constructs (activity and participation) within the ICF model is relatively straightforward. However, the distinction between activity and participation is contextual and somewhat subjective. For example, the behaviour of 'walking for 5 minutes' should be coded as activity, as it is the execution of a task or action by an individual that could be performed in an idealised situation (such as on a treadmill during a health-care assessment). However, the behaviour of 'walking to work for 5 minutes' could be coded as participation as it relates to involvement in a 'real world' situation.

In order to identify the ICF constructs measured by the BRAVVO questionnaire, two health psychologists (who had not been involved with the questionnaire development, and had experience of the ICF model) independently coded each of the behaviours contained within the questionnaire (e.g. driving a car) as measuring none, one or more than one of the ICF constructs (impairment, activity, participation).
The research team compared the health psychologists' coding and discussed any disagreements, with reference to the context within which the item was framed, until consensus was achieved.

Results

Participants

Seventeen participants (12 female and five male) who had received treatment for varicose veins (eight had been treated with EVLA, five with foam sclerotherapy and four with surgery) were interviewed. As some interviews were delayed owing to the personal circumstances of participants, time from treatment to interview was more variable than planned (range 8–19 weeks). At interview, the participants' age range was 30–67 years (mean 48.6 years). Six participants were resident in Aberdeen city and the remainder in the surrounding area (including commuter towns and more rural areas). Hence, a reasonable level of diversity was achieved in this sample. Twelve interviews were conducted in an office at the hospital campus; five were conducted in the participants' homes.

Generation of labels (unique descriptors)

For five transcripts selected at random (two from participants who had undergone EVLA, two from foam and one from surgery), two researchers independently proposed labels to describe each identified behaviour. One researcher proposed 22 labels and the other proposed 30 labels. There was considerable overlap between the labels proposed by each researcher. However, some of the labels proposed by one researcher were more specific than those proposed by the other. For example, one researcher labelled going out socially, going to the cinema and going to a restaurant as three separate behaviours whereas the other researcher labelled them as a single behaviour. Following discussion of the proposed labels, 29 labels were agreed (see *Table 67*). Analysis of the text from the remaining transcripts yielded 12 further labels, making a total of 41 labels (see *Table 67*).

Frequencies for each behaviour

For all 17 interview transcripts, two researchers independently allocated each behaviour identified in the transcripts to one of the 41 labels. The level of agreement between researchers was 96%. Four additional labels were generated at this step, resulting in a final total of 45 labels. The number of participants who mentioned each behaviour was summarised in a frequency table. The frequency data (*Table 67*) thus generated were assumed to be an indicator of the relevance or importance of each milestone across the patient sample.[76]

TABLE 67 Behaviour labels identified from interview data: frequency with which each behaviour was mentioned across interviews

Behaviour label	Frequency
Having a bath/shower[a]	15
Full return to normal work/employment[a]	12
Bending leg(s)[a]	11
Driving – general[b]	11
Wearing clothing that exposes the legs[a]	11
Walking long distances (> 20 minutes)[a]	9
Walking short distances (< 20 minutes)[a]	8
Standing still for a long time (e.g. > 15 minutes)[a]	7
Air travel[a]	5
Caring for children[a]	5
Doing housework[a]	5
Going out socially[a]	5
Lifting heavy objects[a]	5
Partial return to normal work/employment[a]	5
Sitting in car[a]	5
Walking – general[b]	5
Driving – long distance[a]	4
Physical activity with children[a]	4
Shopping[a]	4
Swimming[a]	4
Dancing[c]	3
Driving – short distance[a]	3
Golf[c]	3
Hill-walking[c]	3
Kneeling[c]	3
Sitting down/getting up from chair[a]	3
Using gym equipment, e.g. exercise bike[c]	3
Circuit training/going to gym[a]	2
Climbing steps or stairs[c]	2
Getting in and out of car[a]	2
Going to the cinema/theatre[a]	2
Horse riding[a]	2
Running/jogging[a]	2
Sleeping properly/getting to sleep[c]	2
Curling[b]	1
Cutting grass[c]	1
Cycling[a]	1

TABLE 67 Behaviour labels identified from interview data: frequency with which each behaviour was mentioned across interviews (*continued*)

Behaviour label	Frequency
Diving[c]	1
Fully participating in club/organisation activity[c]	1
Going to a restaurant[a]	1
Having friends over[a]	1
Pole dancing[c]	1
Running the home[a]	1
Stand and tan[b]	1
Stretching leg out[c]	1

a Twenty-nine labels proposed from five transcripts analysed initially.
b Four additional labels proposed during the assessment of frequency of each behaviour.
c Twelve additional labels proposed from analysis of 12 transcripts.

Generation of questionnaire items

Based on these frequencies, the researchers agreed on the items to be included in the final questionnaire, sometimes by collapsing labels for infrequently mentioned activities (e.g. the labels for golfing, horse riding and swimming were collapsed into a single label, 'sporting activity or exercise'). Although 'air travel' was mentioned in five interviews, it was not included as a questionnaire item because it was unlikely to be relevant to all potential trial participants. However, if an individual trial participant felt this behaviour was important to them, they could include it in the open behavioural item ('Anything else that you do that is important to you . . .'). The words 'without discomfort' were added to behaviours that patients reported doing during early stages of recovery, when they had noted doing them without discomfort as a milestone.

During the interviews, participants discussed the bandages and compression stockings worn after treatment. Although wearing them was not considered to be a 'milestone' behaviour, interview participants reported being pleased and relieved to be able to stop wearing their stocking. Therefore, it was agreed that a question would be included in the questionnaire about the length of time for which compression stockings were worn.

Designing the Behavioural Recovery After treatment for Varicose Veins questionnaire

The final version of the questionnaire contained 15 behavioural items (two of which gave participants the opportunity to describe a social activity and a physical activity), one open behavioural item, one item about wearing the support stocking and one sentence completion item ('To help my recovery, I . . .').

We developed a standard response format for the 15 behavioural items and the open behavioural item. *Box 2* illustrates the format of the behavioural recovery items and response options; the full BRAVVO instrument is included in the 6-weeks questionnaire contained in *Appendix 1*. For the three items that asked participants about an important social or physical activity, or anything else important to them (the open behavioural item), the response option 'I don't normally do this' was omitted.

The response options for the item about wearing the support stocking were 'not at all', 'day and night for ____ days, then during the day only for ____ days' and a free-text option to record any other pattern of use.

BOX 2 Format of the behavioural recovery questions and response options

Behaviour

☐ I don't normally do this.

☐ I normally do this, but haven't done so since my treatment.

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment.

Preliminary versions of the questionnaire were pilot tested with three patients (who had agreed to take part in the interview study). This pilot testing suggested that the BRAVVO questionnaire was acceptable to participants, and was comprehensible and thus appropriate for self-completion. We did not change the items included in the questionnaire, but minor refinements to the wording and formatting of the questionnaire were made in response to pilot testing.

International Classification of Disability and Function classification of behaviours included in the Behavioural Recovery After treatment for Varicose Veins questionnaire

Box 3 presents the ICF classification of the 15 behavioural items. There was full agreement between the health psychologists on the ICF construct measured by 11 of the 15 behaviours coded. There was partial agreement for two behaviours ('partial return to normal work/employment', 'full return to normal work/employment'), with one health psychologist coding these behaviours as participation and the other coding

BOX 3 International Classification of Disability and Function classification of BRAVVO behavioural items

Behaviours classed as 'activity'

- Bending the leg(s) (without discomfort).
- Lifting heavy objects (without discomfort).
- Moving from a standing to a sitting position (without discomfort).
- Standing still for a long time, i.e. more than 15 minutes (without discomfort).
- Walking short distances, i.e. less than 20 minutes (without discomfort).
- Walking long distances, i.e. more than 20 minutes.
- Having a bath/shower.
- Driving a car.

Behaviours classed as 'participation'

- Doing housework.
- Looking after children.
- Wearing clothes that show the legs.
- Partial return to normal work/employment.
- Full return to normal work/employment.
- Going out socially (such as going to the cinema, theatre, restaurant, etc.).
- Sporting activity or exercise (such as swimming, going to the gym, cycling, running, jogging, horse riding, hill walking, golf, etc.).

them as measuring both activity and participation. There was also partial agreement on a further two behaviours ('doing housework' and 'sporting activity or exercise'), with one health psychologist coding these as activity and the other as both activity and participation. The research team discussed the four behaviours for which there was partial agreement and consensus was achieved that all four measured participation. The rationale for this was that all relate to involvement in an everyday, 'real world' situation. In addition, in the case of 'doing housework' and 'sporting activity or exercise', there is a lack of behavioural specificity of the tasks or actions involved (i.e. housework could involve light dusting or scrubbing floors). This may make responses to them more difficult to interpret in terms of behavioural recovery.

Use of the Behavioural Recovery After treatment for Varicose Veins questionnaire in Comparison of LAser, Surgery and foam Sclerotherapy

Methods

Data collection

As described in *Chapter 3*, we incorporated the BRAVVO questionnaire into the larger CLASS questionnaire administered 6 weeks following treatment. Participants in the CLASS trial were invited to complete this at their 6-weeks follow-up appointment. Participants who failed to attend for their 6-weeks appointment were sent a questionnaire to complete at home.

Statistical analysis

Data from the BRAVVO questionnaire were analysed within an interval-censored time-to-event framework using flexible parametric survival models.[77] For each behaviour item, each participant's response was converted into the number of days to return to the behaviour. If a participant indicated that return to the behaviour was on the day of the procedure, this was assumed to be interval censored between day 0 and day 1. If a participant indicated that return to the behaviour was after a number of weeks, not days, this was assumed to be interval censored between the previous week and the week indicated. For example, if a participant reported 5 weeks, it was assumed that the return to the behaviour took place between 28 and 35 days. If a participant indicated that they had not returned to a behaviour they usually did, they were right censored at 42 days. Participants who indicated that they did not normally do the specific behaviour were not included in analysis of that behaviour. No missing data were imputed.

We reported the number of days for 50% and 90% of participants to return to each behaviour, estimated from the parametric survival models (the 50% value represents the median time to return to that behaviour). This allows extrapolation beyond the 42-day cut-off for behaviours where 90% of participants had not returned to the activity by 42 days.

The models were fitted on the log cumulative hazard scale, using a restricted cubic spline with one knot to model the baseline hazard function. Treatment effects are presented as hazard ratios (HRs) and 95% CIs. All analyses were carried out in Stata 12 (StataCorp LP, College Station, TX, USA).[78] Flexible parametric survival models were fitted using the stpm command.[79]

The item relating to 'anything else that you do that is important to you, not already mentioned' was only completed by 99 participants (12%). These participants described a wide range of behaviours (including cooking, cycling, gardening and yoga) that might be expected to have a different recovery trajectory. For these reasons, we considered it inappropriate to summarise data or calculate HRs for this item.

Comparison of Behavioural Recovery After treatment for Varicose Veins results by randomised group

Foam sclerotherapy versus surgery

Participants randomised to foam sclerotherapy were able to carry out most of the behaviours (both activity and participation behaviours) more quickly than those randomised to surgery (*Table 68*). In general, the median time to return to the activity behaviours was 5 days or fewer for those randomised to foam and up to 9 days for those randomised to surgery. In both groups, there was greater variation in the median time to return to the participation behaviours than the activity behaviours. For all but two of the behaviours, the HRs comparing foam with surgery indicated that return to the behaviour took longer in the surgery arm. The two behaviours for which there was no evidence of a difference in the time to recover between the trial arms were 'having a bath or shower' and 'wearing clothes that show the legs'.

Endovenous laser ablation versus surgery

For seven of the eight activity behaviours, return to the behaviour took longer for those randomised to surgery than for those randomised to EVLA (*Table 69*). Return to the other activity behaviour (having a bath or shower) was quicker after surgery than after EVLA. For six of the seven participation behaviours, return to the behaviour took longer for those randomised to surgery than for those randomised to EVLA. There was no evidence of a difference in time to return to the other participation behaviour (wearing clothes that show the legs).

Endovenous laser ablation versus foam sclerotherapy

There was little difference in the time taken to return to the majority of activity and participation behaviours between those randomised to EVLA and those randomised to foam (*Table 70*). Exceptions to this were walking short and long distances, looking after children and full return to normal work/employment, where return to the activity was longer for the EVLA group than for the foam group.

Compression stockings

We asked how long participants wore their stocking constantly (i.e. day and night); those in the foam arm reported wearing their stocking longer (median 10 days) than those in both the surgery and EVLA arms (median 7 days for each). We also asked about the number of days (or nights) they wore the stocking after they stopped wearing it constantly. We calculated the total number of days that participants wore their stocking (wearing constantly, and then wearing for part of the day or night only); the median time was shortest for foam (12 days) compared with 14 days for EVLA and 17 days for surgery.

Discussion

In this chapter, we have described the development of the BRAVVO questionnaire as an instrument to assess behavioural recovery, and reported findings from the CLASS trial in which the instrument was used. This is a new approach to investigating and describing return to normal activities after treatment of varicose veins which may be useful for more widespread application.

Strengths and limitations of the Behavioural Recovery After treatment for Varicose Veins instrument

The instrument has a number of limitations. First, although care was taken to recruit a diverse sample of participants, this was essentially a self-selected sample of people in one geographical region of the UK, who might not be typical of patients in general. Second, there were constraints associated with developing a questionnaire that would be suitable and relevant for use by a wide range of trial participants but sufficiently short to minimise participant fatigue. Finally, despite pilot testing the questionnaire, the level of missing data was slightly higher for BRAVVO than for other instruments used within CLASS. It may be beneficial to consider if rephrasing the questions or response options, or reformatting the questions, may reduce the level of missing data.

TABLE 68 Behavioural recovery: foam vs. surgery

Questionnaire item	Proportion carrying out activity (%)	Number of days until 50% (and 90%) of participants can carry out activity[a]		HR[b] (95% CI)
		Foam	Surgery	
Activity items				
Bending the legs without discomfort	50	3.0	4.6	**1.38 (1.14 to 1.67)**
	90	14.1	21.3	
Lifting heavy objects without discomfort	50	4.8	9.8	**1.97 (1.59 to 2.44)**
	90	16.9	34.5	
Moving from standing to sitting without discomfort	50	1.9	3.7	**1.63 (1.35 to 1.97)**
	90	9.3	17.5	
Standing still for a long time (> 15 minutes) without discomfort	50	3.9	7.1	**1.67 (1.36 to 2.05)**
	90	15.8	28.7	
Walking short distances (< 20 minutes) without discomfort	50	1.9	4.4	**2.00 (1.65 to 2.42)**
	90	8.2	19.1	
Walking long distances (> 20 minutes)	50	4.5	8.0	**1.76 (1.45 to 2.14)**
	90	15.2	27.1	
Having a bath or shower	50	5.4	4.9	**0.85 (0.70 to 1.03)**
	90	11.4	10.3	
Driving a car	50	4.1	7.0	**1.78 (1.45 to 2.19)**
	90	12.4	21.1	
Participation items				
Doing housework	50	2.1	4.5	**2.10 (1.72 to 2.56)**
	90	7.3	15.7	
Looking after children	50	1.2	3.5	**2.20 (1.61 to 3.00)**
	90	6.2	17.9	
Wearing clothes that show the legs	50	12.4	12.8	**1.03 (0.78 to 1.35)**
	90	56.6	58.7	
Partial return to normal work/employment	50	4.4	9.9	**2.16 (1.72 to 2.72)**
	90	15.4	34.2	
Full return to normal work/employment	50	4.8	11.7	**2.56 (2.05 to 3.21)**
	90	14.9	36.2	
Going out socially	50	7.1	9.3	**1.29 (1.06 to 1.57)**
	90	25.8	34.0	
Sporting activity or exercise	50	15.7	21.8	**1.33 (1.05 to 1.68)**
	90	62.6	86.7	

a The 50% value is equivalent to the median time to return to the activity.
b A HR > 1 shows return to activity took longer in the surgery arm. HRs shown in bold text are statistically significant.

TABLE 69 Behavioural recovery: EVLA vs. surgery

Questionnaire item	Proportion carrying out activity (%)	Number of days until 50% (and 90%) of participants can carry out activity[a]		HR[b] (95% CI)
		EVLA	Surgery	
Activity items				
Bending the legs without discomfort	50	2.7	4.6	**1.49 (1.1 to 1.75)**
	90	12.6	21.3	
Lifting heavy objects without discomfort	50	5.9	9.8	**1.79 (1.39 to 2.27)**
	90	20.5	34.5	
Moving from standing to sitting without discomfort	50	2.2	3.7	**1.56 (1.27 to 1.96)**
	90	10.4	17.5	
Standing still for a long time (> 15 minutes) without discomfort	50	4.8	7.1	**1.41 (1.11 to 1.79)**
	90	20.0	28.7	
Walking short distances (< 20 minutes) without discomfort	50	3.0	4.4	**1.30 (1.04 to 1.61)**
	90	13.2	19.1	
Walking long distances (> 20 minutes)	50	5.6	8.0	**1.53 (1.06 to 1.67)**
	90	19.8	27.1	
Having a bath or shower	50	5.5	4.9	**0.74 (0.59 to 0.93)**
	90	12.8	10.3	
Driving a car	50	4.4	7.0	**1.82 (1.43 to 2.33)**
	90	12.7	21.1	
Participation items				
Doing housework	50	2.5	4.5	**1.89 (1.49 to 2.38)**
	90	8.4	15.7	
Looking after children	50	1.9	3.5	**1.61 (1.15 to 2.27)**
	90	8.8	17.9	
Wearing clothes that show the legs	50	14.6	12.8	**0.97 (0.69 to 1.35)**
	90	75.1	58.7	
Partial return to normal work/employment	50	6.3	9.9	**1.75 (1.33 to 2.27)**
	90	21.1	34.2	
Full return to normal work/employment	50	7.7	11.7	**1.79 (1.37 to 2.27)**
	90	23.5	36.2	
Going out socially	50	6.9	9.3	**1.41 (1.12 to 1.75)**
	90	23.9	34.0	
Sporting activity or exercise	50	14.2	21.8	**1.47 (1.12 to 1.92)**
	90	55.5	86.7	

a The 50% value is equivalent to the median time to return to the activity.
b A HR > 1 shows return to activity took longer in the surgery arm. HRs shown in bold text are statistically significant.

TABLE 70 Behavioural recovery: EVLA vs. foam

Questionnaire item	Proportion carrying out activity (%)	Number of days until 50% (and 90%) of participants can carry out activity[a]		HR[b] (95% CI)
		EVLA	Foam	
Activity items				
Bending the legs without discomfort	50	2.7	3.0	**0.94 (0.75 to 1.17)**
	90	12.6	14.1	
Lifting heavy objects without discomfort	50	5.9	4.8	**1.11 (0.87 to 1.42)**
	90	20.5	16.9	
Moving from standing to sitting without discomfort	50	2.2	1.9	**1.12 (0.90 to 1.40)**
	90	10.4	9.3	
Standing still for a long time (> 15 minutes) without discomfort	50	4.8	3.9	**1.14 (0.90 to 1.44)**
	90	20.0	15.8	
Walking short distances (< 20 minutes) without discomfort	50	3.0	1.9	**1.48 (1.19 to 1.84)**
	90	13.2	8.2	
Walking long distances (> 20 minutes)	50	5.6	4.5	**1.32 (1.05 to 1.66)**
	90	19.8	15.2	
Having a bath or shower	50	5.5	5.4	**1.19 (0.96 to 1.48)**
	90	12.8	11.4	
Driving a car	50	4.4	4.1	**0.95 (0.74 to 1.21)**
	90	12.7	12.4	
Participation items				
Doing housework	50	2.5	2.1	**1.03 (0.82 to 1.29)**
	90	8.4	7.3	
Looking after children	50	1.9	1.2	**1.45 (1.04 to 2.02)**
	90	8.8	6.2	
Wearing clothes that show the legs	50	14.6	12.4	**1.17 (0.83 to 1.64)**
	90	75.1	56.6	
Partial return to normal work/employment	50	6.3	4.4	**1.17 (0.89 to 1.52)**
	90	21.1	15.4	
Full return to normal work/employment	50	7.7	4.8	**1.43 (1.11 to 1.85)**
	90	23.5	14.9	
Going out socially	50	6.9	7.1	**0.88 (0.70 to 1.10)**
	90	23.9	25.8	
Sporting activity or exercise	50	14.2	15.7	**0.80 (0.61 to 1.04)**
	90	55.5	62.6	

a The 50% value is equivalent to the median time to return to the activity.
b A HR > 1 shows return to activity took longer in the EVLA arm. HRs shown in bold text are statistically significant.

Despite these limitations, the BRAVVO questionnaire represents a systematic first step in identifying the behaviours that may be used to monitor recovery, as well as the actions that patients may take to influence their own recovery following treatment for varicose veins. For the first time, it allows researchers to provide meaningful information to patients about their early recovery and what they may expect to achieve after their treatment.

Comparison of LAser, Surgery and foam Sclerotherapy results in the context of previous research

Return to normal activities

In contrast to previous studies,[14,15,29,32,36–38,40] where it appears that participants were asked about return to 'normal activities', 'full activity', 'daily activity' or 'basic physical activities', and/or return to work and sporting activities, the BRAVVO questionnaire asks about specific behaviours, all of which are likely to contribute to 'normal activities', and all of which were identified by patients as important milestones following their treatment. It provides much more specific and meaningful insights into the wide range of aspects of recovery which are important to patients.

Across the specific behaviours included in BRAVVO, there was variation in the median time to return to the behaviour (i.e. the time that it took for 50% of participants to return to the behaviour). For example, the median time for different behaviours varied from 1 day to 15 days in the foam arm, from 2 days to 14 days in the EVLA arm and from 3 days to 21 days in the surgery arm. This suggests that simply asking about generic 'normal activities' (as in previous studies) may miss important differences between different behaviours. This strengthens the rationale for asking about specific behaviours rather than asking a generic question about 'normal activities'. Information about recovery in terms of specific behaviours could be incorporated into guidance for patients regarding what to expect in the post-treatment period.

Previous studies reporting return to 'normal activity' (i.e. using the terms outlined above) have reported median values of up to 3 days following foam,[14,29,32] up to 7 days following EVLA[15,29,32,37,38] and up to 21 days following surgery.[15,29,37,38] For foam, the median time for some of the behaviours asked about in CLASS was 3 days or fewer; for other behaviours, the median time was considerably longer (up to 15 days). For EVLA, the median time for the majority of behaviours we asked about was 7 days or fewer; only two behaviours had a median time greater than this. For surgery, none of the behaviours we asked about had a median recovery time longer than 21 days. Although this might suggest that the BRAVVO questionnaire has captured similar data to the single question used in previous studies, the data from the BRAVVO questionnaire are more informative. This is because it provides data across a range of specific behaviours which have different recovery trajectories.

The distribution of time to return to each of the behaviours indicates that there is a proportion of people who take much longer to return to the behaviour than would be expected. The extent of this delay in recovery is hard to justify, particularly in light of the information and advice that was given in the study patient information leaflet (PIL), where we suggested that participants should aim to get back to all their normal activities as soon as they were able, but that strenuous activity/contact sport should be avoided for 1–2 weeks. There may have been a number of external influences that had an impact on participants' recovery, including misinformation and fear. Although attitudes to recovery and returning to normal activities have changed in secondary care, this may not have filtered into primary care or the 'public knowledge'. Fear of activity or fear of pain caused by activity has been documented following surgery for other conditions.[80,81] It is possible that some people undergoing treatment for varicose veins will experience similar fears and this may limit or restrict activity following their treatment. In addition, anecdotal evidence suggests that many patients fear 'doing damage' to their leg following treatment, and particularly following surgery. These fears may contribute to delays in recovery.

Two previous studies have observed that patients return to normal activities more quickly after foam than after surgery.[14,29] For all but two of the behaviours we asked about in CLASS, we showed a similar pattern of results. The exceptions were wearing clothes that showed the legs and showering/bathing. Our observation about showering and bathing is likely to have occurred as a result of the information contained in the study PIL. Participants undergoing foam sclerotherapy or EVLA were advised to wear their stocking for 10 days constantly (i.e. day and night). Those in the surgery group were advised that their bandages would be removed the day after the operation, after which they should wear a stocking for 10 days, but that it was reasonable to remove the stocking after 4 or 5 days, providing they were active. Following surgery, they were also told that a shallow bath might be possible if they could raise their leg to keep the stocking dry.

In three previous studies,[15,29,37] the time to return to normal activities was shorter following EVLA than following surgery. For all but two of the behaviours we asked about in CLASS, the findings were similar in that those randomised to EVLA could carry out the behaviour more quickly than those randomised to surgery. One of these behaviours was having a bath or shower, and those randomised to surgery were able to do this earlier after treatment than those randomised to EVLA. The likely reason for this, as discussed above, is the information provided in the PIL. Two previous RCTs comparing surgery and EVLA did not find a difference in mean time to return to daily activities,[36,40] and in one further study there was no difference in median time to return to 'basic activity' between surgery and EVLA.[38]

There have been two previous RCTs which showed a quicker return to normal activities in patients undergoing foam sclerotherapy than in patients undergoing EVLA.[29,32] For four of the behaviours we asked about in CLASS (walking short and long distances, looking after children, full return to normal work/employment), participants in the foam arm returned to the behaviour more quickly than participants in the EVLA arm. For all other behaviours, there was no difference between the arms.

Return to work

Two of the behaviours identified in the interview study, and included in the BRAVVO questionnaire, related to return to work/employment (partial return and full return). As might be expected, across all three arms the median time to full return to work was longer than that for partial return to work. In previous studies, return to work is reported as a single item, without any distinction between partial and full return, which may be of substantial importance to patients, their employers and the economy as a whole.[15,29,36–38,40]

The median time to return to either partial or full employment was significantly longer following surgery than either foam or EVLA. Although there was no significant difference in the median time to partial return to employment following foam or EVLA, the median time to return to full employment was significantly longer following EVLA than following foam. This latter finding is perhaps surprising because, in the PIL, the advice about return to work was identical for foam and EVLA. The advice stated that 'most people are able to return to work within two to three days of treatment, but some people go back the following day or even the same day'. That the time to return to work following surgery was longer than for either foam or EVLA is less surprising. The advice in our PIL for surgery stated that people can return to office or sedentary work after 2–3 days, and that most people will be back at work within 1 week after surgery to one leg and 2 weeks after surgery to both legs. It also stated that there is no reason to remain off work for this long, if it can be managed with reasonable comfort.

In addition to the information given in the PIL and by the vascular surgeon about return to work, a number of factors are likely to mediate return to work after treatment for varicose veins. These may include a person's employment status (employed or self-employed), the sickness benefits they are entitled to, the type of work they are employed to do, how long they are 'signed off' for by their doctor and the views of their employer on return to work after an operation.

In CLASS, the median time to full return to normal work/employment following surgery was 11 days. This is within the range previously reported. Studies have reported median times of 4.3,[29] 11.8,[38] 17[15] and 21 days.[37]

For EVLA, the median time to full return to normal work/employment was 7 days; this is within the range previously reported (4–10 days).[15,29,36–38,40]

For foam sclerotherapy, the median time to full return to work/employment was 4 days. In the one previous study that reported the median number of days for return to work, the median time was shorter (2.9 days) than that found in CLASS (partial return 4.4 days, full return 4.8 days).[29]

In our comparison of surgery versus foam sclerotherapy, we showed that there were significant differences in both partial and full return to work in favour of foam. The one previous study reporting this outcome has shown that return to work was quicker following foam than following surgery.[29]

The CLASS trial showed that return to work following EVLA was quicker than following surgery. This is in line with the findings of three previous RCTs.[15,37,38] In the study by Rasmussen *et al.*,[29] there was no difference in median time to return to work between those undergoing EVLA and those undergoing surgery. Two further RCTs did not find a difference in time to return to work;[36,40] however, in these studies mean times were compared rather than median times, and this may not be the most appropriate measure if the distribution is skewed.

In CLASS, there was no difference in time to partial return to work following foam or EVLA, but full return to work was quicker following foam than following EVLA. The one previous study to report a comparison of foam and EVLA in relation to return to work found that it was quicker following foam than following EVLA.[29]

Further development of the Behavioural Recovery After treatment for Varicose Veins questionnaire

The 14 core behavioural items were designed to be scored along a time scale (number of days after treatment to when each behaviour was first performed), and this is how the findings from the CLASS trial are presented. It may be possible to explore the psychometric properties of the instrument and develop a method of producing an overall score for the behavioural items of the questionnaire. Through a systematic process of independent coding of the behaviours contained within the questionnaire by two health psychologists with experience of the ICF model, we have produced data to show that eight of the items measure activity behaviours and seven measure participation behaviours. It may be possible to score these two classes of behaviours as separate subscales.

The results from the application of BRAVVO in the CLASS trial provide useful data for clinicians as they guide patients through their recovery phase. Similar data following treatment for other conditions may also be helpful for both clinicians and patients. Although some of the items in BRAVVO may be transferable to other conditions, we would recommend using similar methods to those described here to identify relevant items to populate other treatment-specific behavioural recovery questionnaires, and the appropriate time frame at which to assess these. During the funding process, there was discussion regarding the most appropriate time point at which to assess behavioural recovery. Although initially planned for the 6-months follow-up, clinical expertise and interview data indicated that, following treatment for varicose veins, it would be more appropriate to collect this type of data at the 6-weeks follow-up. There were two reasons for this. First, the validity of patient recall data was likely to be higher if patients were recalling

events over the previous 6 weeks than over the previous 6 months. Second, variation in recovery was likely to be greater over a period of 6 weeks, as most patients would consider themselves to be fully recovered well before the 6-months follow-up. Hence, BRAVVO data at 6 weeks were likely to have more explanatory value.

Conclusions

Development of the BRAVVO instrument represents a systematic first step in identifying the actions that patients may take to influence their own recovery following treatment for varicose veins, as well as the behaviours that may be used to monitor recovery. Using this questionnaire, we have shown that patients are able to return to a wide range of behaviours more quickly following foam or EVLA than following surgery.

Chapter 9 Trial-based cost-effectiveness analysis

Introduction

The purpose of this chapter is to report on the economic analysis that was conducted using individual participant cost and effect data collected alongside the RCT. Two comparisons were considered for the analysis: (1) foam sclerotherapy versus surgery; and (2) EVLA versus foam sclerotherapy versus surgery. As with the clinical effectiveness analyses, the first comparison was carried out using data from all recruiting centres, whereas the three-arm comparison was based only on data from the eight centres that randomised participants to all three treatment options. The methods utilised are described below and, following this, the results are presented.

Methods

This economic evaluation was constructed as a cost-effectiveness analysis, the measure of effect being QALYs over the 6-month trial follow-up period. The primary economic outcome was expressed as the incremental cost per QALY for each treatment option. QALY (utility) weights were derived from participant responses to the EQ-5D[82] at baseline, 6 weeks and 6 months. However, to test the robustness of the results to the choice of health state utility instrument, and to enable a comparison with the only other published, UK-based economic evaluation in this area,[65] QALYs were also estimated using responses to the SF-36 via the SF-6D scoring algorithm.[83] For each participant, the area under the curve was calculated to determine the QALYs gained. Total NHS, individual participant and indirect costs were estimated for each participant based on resource use data collected on case report forms and participant questionnaires (see *Appendix 1*). Incremental costs and QALYs associated with the alternative treatment options were estimated using GLMs, adjusted for baseline EQ-5D score and the minimisation covariates. A ceiling ratio of £20,000 per QALY (i.e. a treatment was only deemed cost-effective if it cost less than £20,000 per extra QALY gained) was used to determine cost-effectiveness (i.e. the ICER).[28]

Non-parametric bootstrapping[84] was used to generate CIs for the estimated mean incremental costs and effects, and to summarise the uncertainty surrounding the ICERs. To illustrate the uncertainty surrounding the estimates of cost-effectiveness, cost-effectiveness acceptability curves (CEACs) were derived using the bootstrapped estimates of incremental costs and effects. CEACs demonstrate the probability of an intervention being cost-effective at different ceiling ratios of decision-makers' willingness to pay (WTP) per QALY. To test the robustness of results derived from the base-case analysis, key parameters were subjected to deterministic sensitivity analyses. Such analyses examine the effect of estimated or uncertain parameters on the decision.

Unit cost estimation

Unit costs for all resources were obtained for the financial year 2010–11 and were acquired, where possible, from national sources including the *British National Formulary*,[85] NHS Reference Costs (2011)[86] and the Unit Costs of Health and Social Care [Personal Social Services Research Unit (PSSRU) 2011].[87] Where national sources were not available, other sources were utilised, for example finance departments of participating centres.

NHS costs

Total NHS costs included health service resource use associated with initial treatment, all subsequent contact with primary care (e.g. GP contacts) and secondary care contact potentially related to the participants' varicose veins (e.g. hospital admissions, outpatient appointments).

Cost of treatment procedures

All treatment strategies were performed as day-case procedures; however, the locations and settings differed. The unit costs of performing each of the three treatment strategies were estimated using a 'bottom-up' approach. These costs were collected via a centre-specific resource use and costing questionnaire, allowing us to capture resource use not recorded on the trial CRFs, and also to cost the treatment strategies in a centre-specific manner. The additional questionnaire is shown in *Appendix 4*. Information collected included average participant waiting time (before and after treatment), location of treatment and recovery, nursing staff input, equipment use and consumables used for procedures.

The grade of the surgeon or nurse performing each procedure (nurses performed some foam sclerotherapy treatments), and whether or not they were supervised by a consultant, was recorded on the CRF of each participant receiving treatment. For surgery, the grade of the anaesthetist present was recorded. The times of entering and leaving the operating theatre or treatment room were used as a measure of the total time requirement for all staff (including nursing and support staff) present for the procedure. Further information, relating to the numbers of nursing and support staff who were typically present for the different types of procedure and their salary bands, was collected using the centre-specific resource use and costing questionnaire. This staffing information, together with treatment duration times (obtained for individual participants), was combined with national unit cost data (PSSRU 2011)[87] to estimate the total cost of staff time for each procedure. The unit costs applied for each grade of staff are presented in *Table 71*.

TABLE 71 Unit cost of staff time inputs

Staff	Unit cost per hour (£)	Cost per minute (£)	Source
Nursing staff			
Band 2	20	0.34	PSSRU (2011)[87]
Band 3	24	0.40	PSSRU (2011)[87]
Band 4	30	0.50	PSSRU (2011)[87]
Band 5	82	1.37	PSSRU (2011)[87]
Band 6	107	1.78	PSSRU (2011)[87]
Band 7	129	2.15	PSSRU (2011)[87]
Band 8b (consultant nurse)	147	2.45	PSSRU (2011)[87]
Medical staff			
Foundation Year 1	33	0.55	PSSRU (2011)[87]
Foundation Year 2 core trainee, CCT	42	0.69	PSSRU (2011)[87]
Specialty trainee	59	0.99	PSSRU (2011)[87]
Staff grade	95	1.59	PSSRU (2011)[87]
Associate specialist	131	1.88	PSSRU (2011)[87]
Consultant medical	136	2.27	PSSRU (2011)[87]

CCT, certificate of completion of training.

An extensive list of minor consumables was generated from the trial centre which had recruited most participants and this cost was applied directly to all procedures. However, major consumables and items of capital equipment (which could have a significant impact on overall costs) were collected from a number of participating centres. An overview of the costing approach is described below.

Capital equipment was costed by asking participating centres to report the current market price for major equipment items used. Two major pieces of capital equipment – duplex ultrasound machines and laser generators – were required for foam sclerotherapy and EVLA treatments. Centres reported using Sonosite Micromaxx® or Sonosite M-turbo® ultrasound machines (Sonosite, Inc., Bothell, WA, USA); laser machines reported were Fotona Lasers XP-2® (Fotona, San Clemente, CA, USA) and Biolitec Lasers® (Biolitec, East Longmeadow, MA, USA). However, centres offering EVLA reported receiving laser machines on loan from suppliers. Because the NHS did not incur a cost for any laser generator, no cost was applied for the usage of this capital item in the base-case analysis (a sensitivity analysis was conducted to test this assumption). The initial outlay costs of duplex ultrasound machines were annuitised over the expected serviceable working life of these devices, using an annual depreciation rate of 3.5% to account for the opportunity cost of the investment over time. The estimated equivalent annual cost was then divided by an estimate of annual patient throughput to give an estimated cost per use of £8.78.

The unit costs of staff time incorporated an allocation of overhead and capital (building space) costs attributable to individual grades of staff, but there was nevertheless some concern that these unit costs would not fully capture the opportunity cost associated with procedures which utilised operating theatres. All surgical procedures for the GSV and SSV were performed in an operating theatre. Therefore, a secondary analysis was undertaken, whereby an extra allocated cost per minute for use of an operating theatre was applied to procedures for which a theatre was stated as the main location for treatment. An additional cost of £3.64 per minute, derived from Information Services Division (ISD) data,[88] was calculated from the total allocated costs attributable to theatre use divided by total theatre operating time at three large teaching hospitals in Scotland. These allocated costs include the cost of theatre equipment and cleaning of consumables. Therefore, for the secondary analysis, the bottom-up estimated costs of equipment use and cleaning were dropped from total cost estimates for procedures carried out in theatre (to avoid double counting).

Foam sclerotherapy

Foam sclerotherapy was, for the most part, performed in a clinic setting. The nursing staff requirements reported for this procedure varied from one to two nurses (band 5 or 6), with some centres also reporting the presence of a health-care assistant or nurse runner.

Foam sclerotherapy treatment involves the injection of a foam sclerosant into the affected vein(s), guided by ultrasound. The unit cost of the ultrasound machine usage was also incorporated for each treatment session. One centre reported using a micropuncture kit for venous access, whereas others reported using an intravenous cannula (a small, flexible plastic tube that is inserted into the vein). The cost of the micropuncture kit (which incurs a higher cost than the intravenous cannula) was only applied to the centre that reported using it. *Table 72* shows the unit costs, over and above staff time, of items of resource use included in the cost calculation for foam sclerotherapy treatment.

Endovenous laser ablation

Centres reported varied locations for performing EVLA. These included outpatient clinic room, treatment room, short-stay ward and day-case theatre (a minority of centres reported performing procedures here). All procedures were performed under local anaesthetic, regardless of location. The unit cost of staff time was estimated as outlined in *Table 71*.

Disparities were evident among centres performing EVLA in terms of staff (additional to the surgeon) present at the procedure. On average, centres reported the presence of two additional staff for procedures performed in a clinic or treatment room setting, whereas those that used a theatre or short-stay ward to

TABLE 72 Items included in the cost calculation for foam sclerotherapy

Resource use item	Mean unit cost (£)	Assumptions	Source
Foam sclerotherapy	STS 3%: 5.52 per amp	3% used for GSV and SSV	Participating centre (lead centre) (2013)
	STS 1%: 4.54 per amp	1% used for non-truncal varicosities	
Consumables	50.20	Centre using micropuncture kit	Participating centres, resource use and costing questionnaire (2013)
Consumables	26.23	Applied to all centres other than that using micropuncture kit	Participating centres, resource use and costing questionnaire (2013)
Capital equipment (ultrasound machine)	8.78	Per usage	Participating centres, resource use and costing questionnaire (2013)
Preparation cost of clinic/theatre	24.86	Applied to all centres	Clinical opinion (2013), PSSRU (2011)[87]
Recovery cost	1.70	10 minutes in recovery area	Clinical opinion (2013), PSSRU (2011)[87]

amp; ampoule.

perform EVLA reported an average of five additional staff. Additional staff types included theatre nurses, vascular nurse specialists, health-care assistants/support workers, trainee operating department practitioners and nurse runners. Although the base-case analysis incorporated staff present in a centre-specific manner, a sensitivity analysis was conducted to assess the impact if EVLA was performed in a clinic or treatment room setting only and adopted a similar staff profile to foam sclerotherapy.

Endovenous laser ablation requires the use of both an ultrasound machine to identify the veins that need treatment, and a laser generator to deliver the energy to the vein via the laser fibre. Although it was assumed that the laser generator would generally be loaned free of charge to the NHS, this still requires the use of a laser fibre. The price of this non-reusable laser fibre (£256) is a key driver in the overall cost of this treatment. *Table 73* shows the unit costs included in the cost calculation for the EVLA procedure. In addition, the section of the resource use and costing questionnaire concerned with EVLA captured the average length of time spent on the ward both before and after the procedure.

Surgery

The staffing requirements for surgery were again costed in a participant-/centre-specific way. All procedures are carried out in an operating theatre under general or epidural/spinal anaesthetic. Surgery also requires additional staff time to look after the patient in the recovery room and recovery ward after the procedure, during recovery from anaesthesia.

TABLE 73 Items included in the cost calculation for EVLA

Resource use item	Unit cost (£)	Assumptions	Source
Consumables	65.06	Applied to all centres	Participating centre (lead centre) (2013)
Laser fibre	256	Includes catheter and guide wire	Participating centre (lead centre) (2013)
Capital equipment (ultrasound machine)	8.78	Per usage	Participating centres, resource use and costing questionnaire (2013)
Preparation cost of clinic/theatre	23.78	Applied to all centres	Clinical opinion (2013), PSSRU (2011)[87]
Recovery cost	31.85	Estimated from resource use and costing questionnaire	Clinical opinion (2013), PSSRU (2011)[87]

Centres specified a range of different nursing and support staff present for this procedure, with an average of five staff in addition to the surgeon and anaesthetist. These staff included anaesthetic nurses, scrub nurses, assistant scrub nurses, health-care assistants, nurse runners, operating department practitioners and recovery nurses.

The main capital equipment items required for the surgical procedure are the electrocardiograph (ECG), pulse oximeter and non-invasive blood pressure monitor. A cost per patient was calculated in a similar way to that for use of the ultrasound machine.

Time spent by participants in the recovery room after the procedure was also recorded on the CRFs. It was assumed that the cost of the recovery room time would include half the time of a band 5 nurse, while further time spent on a recovery ward after leaving the recovery room would incur one-quarter of the time of a band 5 nurse. *Table 74* outlines the cost items, over and above the staffing costs for the procedure and recovery room time, required for the estimation of the total costs of surgery. Information was collected from the additional resource use and costing questionnaire on the average time spent by participants on the day-case ward before and after treatment.

Follow-up health service use costs

Data on the use of secondary health-care services (hospital admissions and outpatient attendances) were collected using a combination of clinical assessment forms (completed at 6 weeks and 6 months) and a data abstraction form completed by the research nurse at each centre based on each participant's medical records. Data on the use of primary care services over the follow-up period were collected from the 6-months, patient-completed questionnaire. The clinical assessment and data abstraction forms captured information regarding any hospital admissions and any additional treatment to the study leg (outside the CLASS trial protocol). Reported hospital admissions were reviewed by clinicians on the trial team, and those identified as possibly related to treatment were costed using the appropriate NHS reference cost (Department of Health 2011).[86] The average costs of the treatment strategies, derived from the bottom-up micro-costing of treatment strategies, were applied for additional reported varicose vein treatments to the study leg that were not recorded in the CLASS treatment CRFs.

Unit costs from nationally available data were used to cost primary care contacts (*Table 75*). Participants were asked whether or not they had been in contact with a GP as a result of their varicose veins (visit to the GP, telephone call and/or GP home visit), and if so, how many contacts they had over the previous 6 months. Questions relating to appointments with other health-care workers (e.g. community or practice nurse, NHS physiotherapist, NHS occupational therapist) as a result of varicose veins were also recorded and costed in a similar manner.

TABLE 74 Items included in the cost calculation for surgery

Resource use item	Unit cost (£)	Assumptions	Source
Consumables	159.56	Applied to all centres	Participating centre (lead centre) (2013)
Capital equipment (ECG, pulse oximeter and blood pressure monitor)	4.15	Per usage	Participating centres, resource use and costing questionnaire (2013)
Preparation cost of theatre	31.36	Applied to all centres	Clinical opinion (lead centre) (2013), PSSRU (2011)[87]
Time on ward after leaving the recovery room	47.60	One-quarter of the time of a band 5 nurse for 140 minutes	Participating centres, resource use and costing questionnaire (2013), PSSRU (2011)[87]

TABLE 75 Primary care unit costs

Practitioner	Unit cost (£)	Assumption	Source
GP clinic visit	36	11.7-minute surgery visit	PSSRU (2011)[87]
GP home visit	120	Home visit lasting 23.4 minutes (including travel time)	PSSRU (2011)[87]
GP telephone conversation	22	7.1-minute telephone conversation	PSSRU (2011)[87]
Community nurse	18.67	20-minute visit	PSSRU (2011)[87]
Practice nurse	12	GP nurse	PSSRU (2011)[87]
NHS physiotherapist	17	30-minute clinic visit	PSSRU (2011)[87]
NHS occupational therapist	17	30-minute clinic visit	PSSRU (2011)[87]

Follow-up assessment and outpatient costs

An additional outpatient follow-up assessment cost was applied to all participants who received just one treatment of EVLA or foam sclerotherapy. This was done because the CLASS trial was designed to assess the clinical effectiveness and cost-effectiveness of EVLA and foam sclerotherapy with additional further foam sclerotherapy as required. Participating centres reported that it is normal practice for all participants, having received initial treatment with EVLA or foam sclerotherapy, to return for a follow-up appointment to assess the need for further treatment. We applied the cost of an outpatient follow-up attendance (£123) with duplex scan (£53) for all participants in the data set who attended their 6-weeks clinical assessment following one treatment session with EVLA or foam sclerotherapy. For participants who had further treatment following initial treatment with EVLA or foam sclerotherapy, we assumed that this was done at their planned follow-up appointment when the decision was made that it was needed, and so no additional clinical assessment cost was applied to these participants. However, because the majority of participants receiving EVLA or foam sclerotherapy as their initial treatment did not receive any subsequent treatment in the trial, we also carried out a sensitivity analysis in which routine follow-up costs were excluded for all participants. As surgery patients would not routinely be seen at 6 weeks after surgery in normal NHS practice, no costs were attributed for this.

In addition, some participants incurred unplanned outpatient appointments during the 6-month follow-up period, which could potentially have been related to their varicose veins treatment (e.g. surgical and medical outpatient appointments). These were costed using the appropriate NHS reference cost (Department of Health 2011)[86] and included in the analysis.

Total NHS cost

The total cost to the health service was computed by summing the estimated treatment and follow-up costs for each participant in the data set. If one of the component costs was missing, then that participant was dropped from the analysis of complete case data. Two total NHS cost variables were computed, one excluding the additional cost applied to procedures carried out in theatre, and one which included this extra cost. This was to ensure that the opportunity cost associated with procedures which utilised operating theatres was accurately captured.

Costs directly incurred by the participant and indirect costs

Individual participant costs were estimated based on responses to the health-care utilisation questions included in the 6-months questionnaire. Individual participant costs comprised three main elements: self-purchased health care; travel costs of making return visit(s) to NHS health-care provider(s); and the time costs incurred while travelling to and attending NHS care. The estimation of travel costs required information from participants regarding the number of visits to, for example, their GP, and the unit cost of making a return journey to each type of health-care provider. The cost of participant time was estimated in a similar manner. Participants were asked how long they spent travelling to and attending their last visit to

each type of health-care provider. They were asked what activity they would otherwise have been doing (e.g. paid work, housework, leisure activities) had they not attended the health-care provider, enabling a calculation of the opportunity cost associated with their health-care contact. These data were presented in natural units and costed using standard economic conventions, such as the Department of Transport estimates for the value of leisure time.[89] *Table 76* presents the unit costs used to value participant time in the analysis. These unit time costs were combined with estimates of the number of health-care contacts derived from the 6-months questionnaire. Costs were also acquired for any additional private health care that participants had for their varicose veins which was recorded in the 6-months questionnaire.

Indirect costs were defined as the production losses resulting from treatment when the participant was unable to return to normal activity. Information regarding participants' recovery was collected in the 6-weeks questionnaire. Included in this section was the length of time to return to normal activities, comprising doing housework, looking after children and partial or full return to normal work/employment. As with the calculation of participant time cost, these data were recorded in natural units and costed using standard economic conventions (see *Table 76*). This estimate gave the cost of days lost associated with the participants' health care. Individual participant, indirect and NHS costs were combined and a further analysis was conducted.

Health outcome measures

The EQ-5D and SF-36 were completed by participants at baseline, 6 weeks and 6 months using a self-completion questionnaire, ensuring that all movements in HRQoL which occurred during the follow-up period were accurately captured. A preference-based index score was derived for each participant's response to the EQ-5D using the UK population time trade-off tariff,[82] and responses to the SF-36 were converted into a preference-based index score using the SF-6D scoring algorithm.[83] Although both these index scores are anchored on full health (1) and death (0), making them suitable for estimating QALYs for individual participants, the EQ-5D is the instrument favoured by NICE for this purpose. Therefore, the EQ-5D was used to estimate participant QALYs in the base-case economic analysis.

Quality-adjusted life-years for each participant were computed by assuming that changes in utility between measures at adjacent time points follow a straight line between the points. The average utility over each time period (baseline to 6 weeks, and 6 weeks to 6 months) was calculated and multiplied by the duration of that time to compute the corresponding QALYs. If an EQ-5D value was missing for a participant at any time point, that patient was dropped from the analysis of complete case data.

TABLE 76 Unit costs applied to participant time associated with treatment and health service utilisation

Activity	Cost per hour (day), £	Assumption	Source
Paid work	12.62 (100.96)	Median hourly earnings, excluding overtime	ONS (2011)[90]
Housework	10.10 (80.77)	Annual salary of £21,000	NHS Pay Review Body 2012 Report[91]
Child care	12.62 (100.96)	Median hourly earnings, excluding overtime	ONS (2011)[90]
Caring for relative/friend	12.62 (100.96)	Median hourly earnings, excluding overtime	ONS (2011)[90]
Unemployed	4.46 (35.68)	Values of non-working time	TAG (2011)[89]
Voluntary work	12.62 (100.96)	Median hourly earnings, excluding overtime	ONS (2011)[90]
Leisure activities	4.46 (35.68)	Values of non-working time	TAG (2011)[89]

ONS, Office for National Statistics; TAG, transport analysis guidance.

Statistical analysis of economic data

The economic analysis was conducted by intention to treat. Cost, QALY and resource use data were summarised and analysed using Stata version 12.1.[78] The mean incremental costs associated with EVLA and foam sclerotherapy versus surgery were estimated using a GLM, with adjustment for minimisation variables (age < 50 years, sex, SSV or GSV, unilateral or bilateral) and participant baseline values as appropriate (e.g. baseline utility scores). A GLM model allows for heteroscedasticity by specifying a distributional family, which reflects the relationship between the mean and variance.[84] To test the appropriate family, a modified Parks test was conducted. The test identified the Gamma family, which allows for right skewness in the cost data and assumes that the variance is proportional to the square of the mean, as appropriate. The specification of a link function is also required for a GLM model; this specifies the relationship between the set of regressors and the conditional mean.[84] The link test recognised the identity link as the appropriate link function. The identity link leaves the interpretation of the coefficients unchanged from that of the ordinary least squares (OLS) regression, in that the covariates act additively on the mean. To further ensure that the correct model was specified, the Akaike information criterion (AIC) was used to assess the model fit. An OLS regression was implemented to estimate mean incremental differences in QALYs associated with EVLA and foam sclerotherapy, adjusting for minimisation variables and participant baseline values in a similar manner. To account for the potential lack of independence in costs and outcomes for participants within centres, cluster robust standard errors and CIs are reported for the estimated mean incremental costs and effects.

To characterise the uncertainty surrounding the estimates of incremental cost-effectiveness, clustered bootstrapping was used to generate 1000 estimates of the mean costs and effects by treatment allocation group. CEACs were generated using these 1000 estimates, using the net monetary benefit (NMB) approach. The NMB associated with a given treatment option is given by the formula:

$$\text{NMB} = (\text{effect} \times \text{Rc}) - \text{cost}, \quad (1)$$

where effects are measured in QALYs and Rc is the ceiling ratio of WTP per QALY. Using this formula, the strategy with greatest NMB was identified for each of the 1000 bootstrapped replicates of the analysis, for different ceiling ratios of WTP per QALY. Plotting the proportion of bootstrap iterations favouring each treatment option (in terms of the NMB) against increasing WTP per QALY produces the CEAC for each treatment option. These curves present graphically the probability of each treatment strategy being considered optimal at different levels of WTP per QALY gained.

Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted, focusing on the impact of altering key costing assumptions and restricting the comparisons to subgroups of the population. All the sensitivity analyses were conducted with the exclusion of additional operating theatre costs. We assessed the impact of excluding the routine follow-up costs (the cost of an outpatient follow-up appointment and duplex ultrasound scan) following EVLA and foam sclerotherapy. This was to reflect that the majority of participants receiving these treatment strategies as their initial treatment did not receive any further foam sclerotherapy treatment in the trial. We tested the impact of restricting the comparisons to subgroups of the population (e.g. those with unilateral disease only and also those with unilateral disease and involvement of the GSV only). The impact of using the SF-6D to calculate QALYs was assessed. Two further sensitivity analyses were conducted for the three-arm comparison, assessing the impact on the results for EVLA of (i) incorporating a staff profile if the procedure was performed in a clinic/treatment room setting, and (ii) including the cost per usage of the laser generator.

As the base-case cost-effectiveness analyses were conducted for participants with complete cost and QALY data, multiple imputation was carried out using Stata's chained equations procedure to replace each missing resource use, cost and EQ-5D variable with a different plausible value in 10 imputed data sets.[78] Ten imputations was found to produce stable estimates of incremental costs and effects. The cost and QALY analysis models were then run across the 10 imputed data sets and combined using Rubin's rules[92] to produce a single set of results. Multiple imputation was conducted on both the full data set and the data that remained when those participants receiving no treatment and follow-up (and thus incurring no costs) were dropped.

Results

The results from the two-arm comparison (foam sclerotherapy vs. surgery) are described below, and following this, the results from the three-arm comparison (EVLA vs. foam sclerotherapy vs. surgery) are presented.

Foam sclerotherapy versus surgery

Resource use and costs

Table 77 documents the main components included in the treatment cost estimation for participants (randomised to foam sclerotherapy or surgery). Of the 286 participants randomised to foam sclerotherapy, 268 presented for their allocated treatment, although two of these participants were found to be unsuitable for foam sclerotherapy treatment. Ten participants randomised to foam sclerotherapy received either surgery ($n = 4$) or EVLA ($n = 6$). Eleven participants randomised to foam sclerotherapy received no treatment within CLASS. The mean number of treatments for those participants receiving foam sclerotherapy was 1.12. The surgical arm included 289 participants. Of these, 253 received their allocated treatment, but 19 received treatment in the form of foam sclerotherapy ($n = 11$) or EVLA ($n = 8$). The mean number of foam sclerotherapy treatments among those receiving this treatment modality was similar to that in the foam group (1.09 treatments). Twenty-one participants randomised to surgery received no treatment within CLASS.

For participants randomised to foam sclerotherapy, the mean cumulative time spent receiving this treatment modality was 29.7 minutes. This was considerably shorter than the time spent by participants receiving surgery in the surgery group (64.56 minutes). Staff costs for the procedure were derived from the duration times and the grades and numbers of staff present for each procedure; therefore, the overall staff costs were considerably higher in the surgery arm (£599 compared with £144 for foam sclerotherapy).

A considerable difference was also evident between the foam sclerotherapy and surgery arms in terms of recovery, consumable and theatre use costs. The estimated total mean treatment costs, inclusive of staff costs, consumables, equipment use, clinic/theatre preparation and recovery time costs, amounted to £241 for foam sclerotherapy and £891 for surgery.

Table 78 shows follow-up resource use and costs over the 6-month follow-up period, by treatment allocation group. Resource use and costs were generally similar for the foam sclerotherapy and surgery arms, although unplanned outpatient appointments were slightly more frequent in the foam sclerotherapy arm and primary care use was slightly higher in the surgery arm. Attendance at the 6-week and 6-month assessments was > 90% in both arms; however, only the cost of the 6-week assessment was included in the economic analysis for participants receiving foam sclerotherapy. There were no reports of hospital admissions related to treatment in the foam sclerotherapy group, and the number reporting this outcome in the surgical group was low (0.02 of those randomised to surgery).

TABLE 77 Treatment costs by treatment allocation group

Treatment details	Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	286			289		
Treatment received						
Presented for foam (*n*, %)	268	93.7		11	3.8	
Number of foam treatments (*n*, mean, SD)	268	1.12	0.35	11	1.09	0.30
Presented for surgery (*n*, %)	4	1.4		253	87.5	
Presented for EVLA (*n*, %)	6	2.1		8	2.8	
No recorded treatment (*n*, %)	11	3.9		21	7.3	
Treatment durations[a]						
Cumulative procedure time (minutes)						
Foam sclerotherapy (*n*, mean, SD)	261	29.70	16.53	288	1.10	7.08
Surgery (*n*, mean, SD)	285	0.78	7.63	270	64.56	33.67
EVLA (*n*, mean, SD)	283	0.62	6.05	288	1.20	7.89
Treatment costs						
Staff procedure costs						
Foam sclerotherapy (*n*, mean, SD)	261	£144	£87	288	£5	£36
Surgery (*n*, mean, SD)	285	£8	£75	270	£599	£340
EVLA (*n*, mean, SD)	283	£4	£37	288	£8	£50
Recovery time costs (*n*, mean, SD)	285	£3	£9	271	£72	£34
Consumable costs (*n*, mean, SD)	286	£44	£52	289	£150	£54
Theatre use (*n*, mean, SD)	260	£23	£50	269	£238	£121
Equipment costs (*n*, mean, SD)	286	£9	£4	289	£4	£2
Preparation costs (*n*, mean, SD)	286	£27	£10	289	£29	£9
Total treatment costs						
Foam sclerotherapy (*n*, mean, SD)	261	£218	£104	288	£8	£49
Surgery (*n*, mean, SD)	285	£10	£103	270	£859	£429
EVLA (*n*, mean, SD)	283	£8	£76	288	£17	£108
Total staff procedure costs (*n*, mean, SD)	257	£159	£107	268	£617	£321
Total treatment costs[b] (*n*, mean, SD)	257	£241	£142	268	£891	£391

a Treatment duration times are the mean times of all patients randomised to the treatment strategy.
b Total treatment costs exclude the additional cost for the use of theatre.

TABLE 78 Follow-up resource use and costs by treatment allocation group

Post-treatment care costs	Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	286			289		
Primary care						
GP consultations (*n*, mean, SD)	234	0.36	0.74	213	0.56	1.19
Other health professional consultations (*n*, mean, SD)	234	0.28	1.96	213	0.44	1.05
Total cost of GP consultations (*n*, mean, SD)	234	£13	£27	213	£20	£42
Total cost of consultations (other health professionals) (*n*, mean, SD)	234	£4	£30	213	£6	£15
Total primary care costs (*n*, mean, SD)	234	£17	£40	213	£26	£44
Secondary care (planned)						
Attendance at 6-week assessment[a] (*n*, mean, SD)	265	260	98.1	251	241	96.0
Attendance at 6-month assessment[b] (*n*, mean, SD)	250	230	92.0	235	217	92.3
6-week assessment cost[a] (*n*, mean, SD)	265	£173	£24	251	£169	£35
6-month assessment cost[b] (*n*, mean, SD)	250	£162	£48	235	£163	£47
Secondary care (unplanned)						
Unplanned medical/surgical outpatient appointments (*n*, mean, SD)	286	0.25	1.15	289	0.20	0.77
Cost of unplanned outpatient appointments (*n*, mean, SD)	286	£35	£138	289	£29	£93
Admissions (*n*, mean, SD)	272	0	0	254	0.02	0.12
Admission costs (*n*, mean, SD)	272	£0	£0	254	£5	£42

a One follow-up attendance is retained as a cost following foam sclerotherapy and EVLA in the economic analysis.
b Research costs removed from the economic analysis.

Table 79 documents the total mean NHS costs associated with both treatment strategies to 6-months follow-up. These are reported for both the primary (excluding the additional cost for operating theatre use) and secondary (including the extra cost for operating theatre use) analysis of NHS costs. For the primary analysis, the mean total cost for those randomised to foam sclerotherapy was £458, compared with £1057 for those randomised to surgery. When the additional cost of theatre (£3.64 per minute in the operating theatre) is included, the mean total cost of foam sclerotherapy increases slightly to £479, and the mean total cost of surgery increases to £1314.

Health outcomes: European Quality of Life-5 Dimensions and Short Form questionnaire-6 Dimensions

The EQ-5D and SF-6D results are summarised by treatment allocation group in *Table 80*. These data showed a general improvement in generic HRQoL in both foam sclerotherapy and surgery treatment allocation groups between baseline and 6 weeks, and between 6 weeks and 6 months. The increase in

TABLE 79 Total NHS costs by treatment allocation group

NHS costs	Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	286			289		
Total NHS costs (primary analysis) (*n*, mean, SD)	206	£458	£201	196	£1057	£327
Total NHS costs (secondary analysis) (*n*, mean, SD)	206	£479	£215	196	£1314	£399

TABLE 80 Health state utilities by treatment allocation group

HRQoL	Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	286			289		
EQ-5D						
Baseline (*n*, mean, SD)	279	0.803	0.179	279	0.783	0.178
6 weeks (*n*, mean, SD)	242	0.860	0.161	227	0.876	0.169
6 months (*n*, mean, SD)	235	0.895	0.174	206	0.881	0.202
Total QALYs (*n*, mean, SD)	217	0.435	0.072	188	0.432	0.082
SF-6D						
Baseline (*n*, mean, SD)	272	0.767	0.122	269	0.754	0.128
6 weeks (*n*, mean, SD)	240	0.774	0.121	218	0.765	0.116
6 months (*n*, mean, SD)	227	0.805	0.122	199	0.802	0.127
Total QALYs (*n*, mean, SD)	202	0.392	0.054	166	0.390	0.052

the EQ-5D score between baseline and 6 weeks was more marked in the surgery arm, whereas the improvement was greater in the foam sclerotherapy arm between 6 weeks and 6 months. Overall, the QALYs accrued over 6 months were slightly lower in the surgery arm, although this was likely to have been due to a slight imbalance in EQ-5D scores at baseline.

Incremental cost-effectiveness: primary analysis

It was found that surgery was associated with a slight gain in QALYs following adjustment for baseline EQ-5D and minimisation variables, but it was also associated with a significantly higher health service cost than foam sclerotherapy (*Table 81*). Therefore, foam sclerotherapy was less costly than surgery (cost saving), but at the expense of HRQoL, which was lower.[84] The ICER was £102,106, which represents the cost saving per QALY lost with foam sclerotherapy versus surgery. NICE generally judges an intervention as being cost-effective if the additional cost required to fund it is < £20,000 per QALY gained (i.e. the ICER is < £20,000). Conversely, assuming equal value placed on a QALY gained and a QALY lost, one would require an ICER > £20,000 of cost savings before the decision-maker would be willing to sacrifice one QALY. As the ICER is above the threshold value, based on this decision rule, foam sclerotherapy would have a favourable ICER.

To explore the uncertainty surrounding the estimate of cost-effectiveness, a CEAC was derived using the results of 1000 bootstrapped replicates of the estimated mean incremental costs and effects. *Figure 4* shows the empirical estimate of the joint distribution of mean incremental costs and effects (for foam sclerotherapy vs. surgery) obtained using the results of the bootstrap replicates. The estimates indicate that foam sclerotherapy is significantly less costly, with a non-significant tendency to produce fewer QALYs than surgery. Applying a ceiling WTP ratio of £20,000 per QALY, *Figure 5* illustrates that, when using the EQ-5D as the measure of outcome, foam sclerotherapy has a 99.8% probability of being considered cost-effective at 6 months. The sensitivity of these findings to missing data is assessed using multiple imputation (see *Deterministic sensitivity analysis*).

TABLE 81 Incremental cost-effectiveness: foam sclerotherapy vs. surgery

Intervention	Incremental costs (95% CI), £	Incremental QALYs (95% CI)	ICER (£)
Surgery	–	–	–
Foam sclerotherapy	−602 (−740 to −464)	−0.006 (−0.021 to 0.009)	102,106

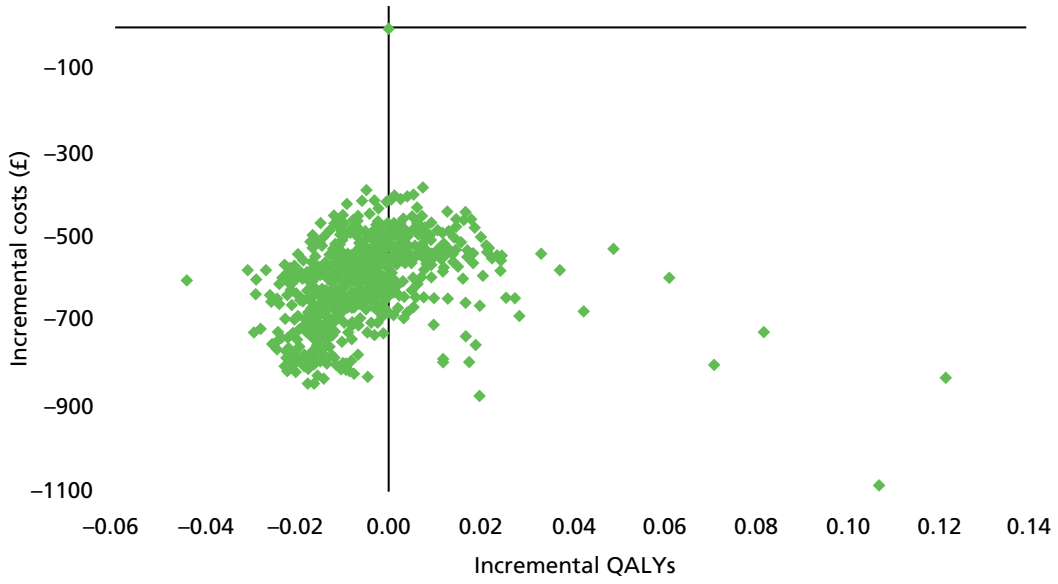

FIGURE 4 Incremental cost-effectiveness scatterplot for foam sclerotherapy vs. surgery at 6 months.

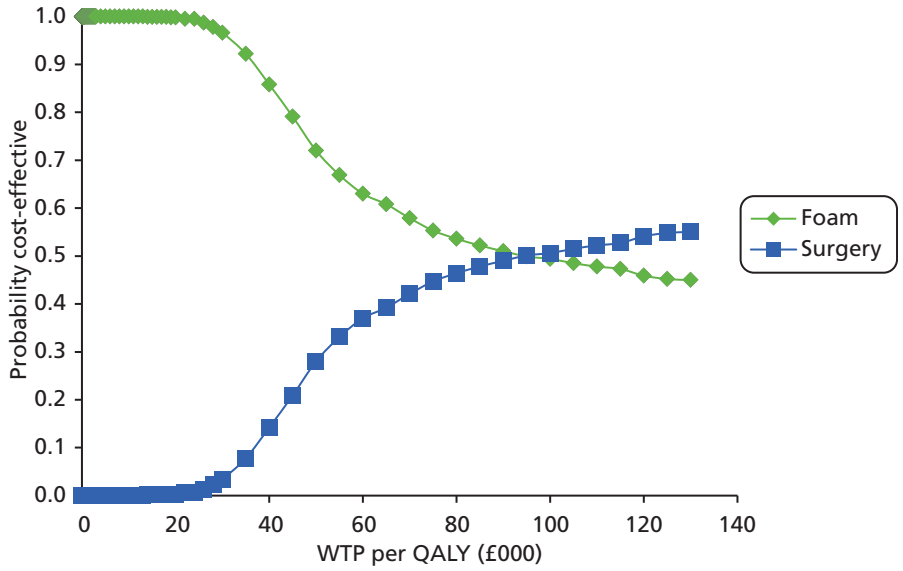

FIGURE 5 Cost-effectiveness acceptability curves for foam sclerotherapy vs. surgery at 6 months.

Incremental cost-effectiveness: secondary analysis

The secondary analysis (incorporating an additional cost for the use of an operating theatre) reinforces the findings of the primary analysis, increasing the cost saving associated with foam sclerotherapy. Under these alternative costing assumptions, the ICER increases to £142,973, representing the cost saving per QALY lost for foam sclerotherapy versus surgery (*Table 82*).

Similar to the primary analysis, although the cluster falls further below zero on the cost axis (i.e. cost saving), *Figure 6* illustrates that foam sclerotherapy has a significantly lower cost with a non-significant tendency to produce fewer QALYs. *Figure 7* shows that when the additional cost of operating theatre use is included, foam sclerotherapy retains the higher probability of being considered cost-effective at 6 months up to the ceiling WTP of > £130,000 per QALY.

TABLE 82 Incremental cost-effectiveness: foam sclerotherapy vs. surgery (secondary analysis)

Intervention	Incremental costs (95% CI), £	Incremental QALYs (95% CI)	ICER (£)
Surgery	–	–	–
Foam sclerotherapy	−843 (−1004 to −682)	−0.006 (−0.021 to 0.009)	142,973

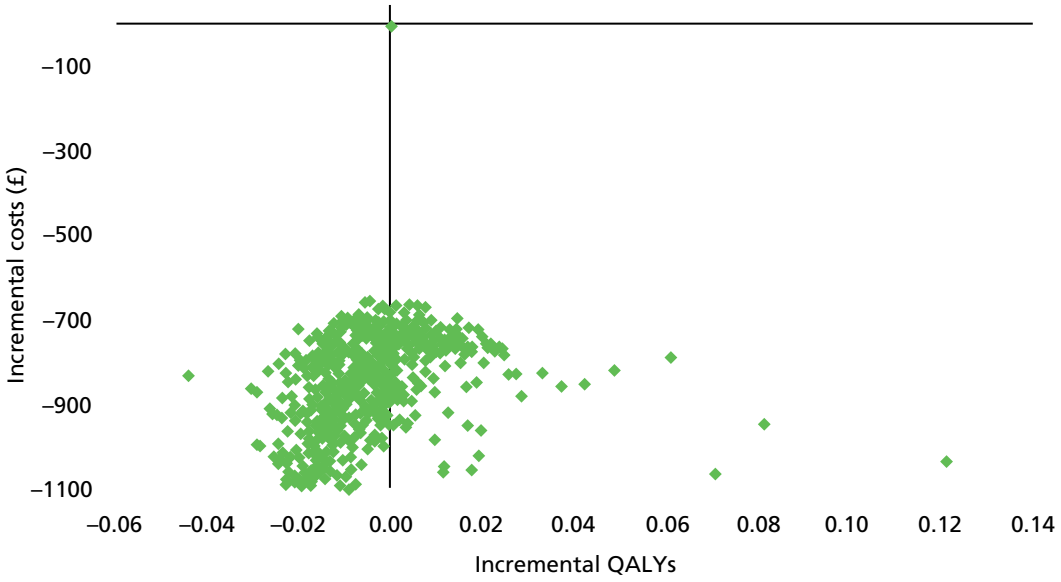

FIGURE 6 Incremental cost-effectiveness scatterplot for foam sclerotherapy vs. surgery, including additional theatre use costs at 6 months.

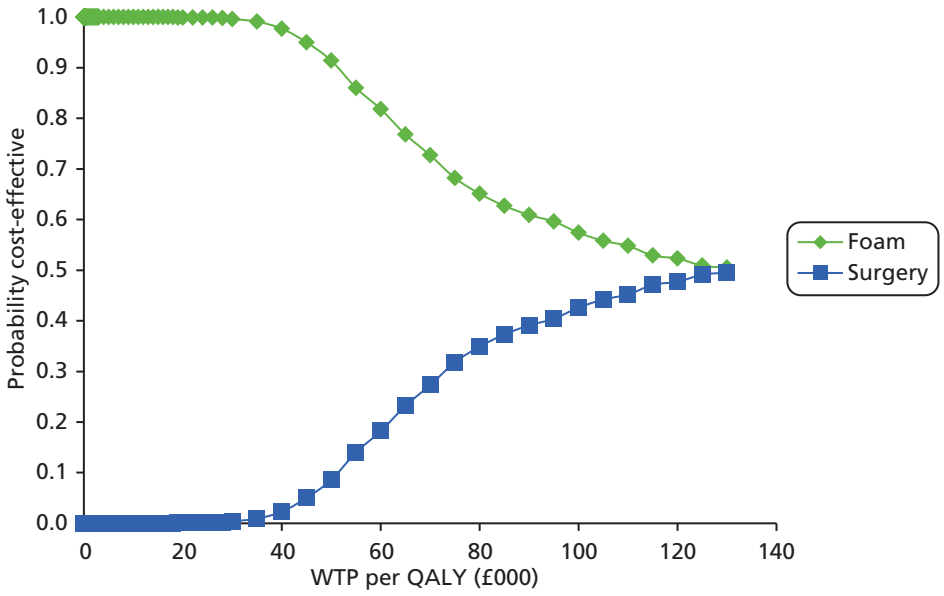

FIGURE 7 Cost-effectiveness acceptability curves for foam sclerotherapy vs. surgery, including additional theatre use costs at 6 months.

Deterministic sensitivity analysis

The overall conclusions drawn from the base-case analysis remain robust to changes in the key costing assumptions and restriction to subgroups (*Table 83*). Under the first adjustment (excluding routine follow-up costs for foam sclerotherapy), the ICER increases, representing a greater cost saving per QALY lost. Scenario 2 (restricting the analysis to participants with unilateral disease only) has a broadly similar ICER value to that obtained in the base-case analysis. However, by restricting the analysis to participants with unilateral disease and GSV involvement only, the ICER, and hence the case for cost-effectiveness, reduces considerably, with a lower cost saving per QALY lost. A greater cost saving per QALY lost is evident when the SF-6D is used to calculate QALYs. The results appear robust to the missing data, with similar results obtained using multiple imputation to replace missing cost and utility values. For all analyses, the ICER remains above a threshold value of £20,000–30,000 per QALY. These analyses demonstrate that foam sclerotherapy remains the preferred option from a cost-effectiveness perspective, a conclusion that remains robust under a range of plausible assumptions.

Endovenous laser ablation versus foam sclerotherapy versus surgery

Resource use and costs

This analysis includes all participants recruited in the eight centres who were randomised to all three treatment options. *Table 84* illustrates the resources used and corresponding costs of treatment by treatment allocation group (EVLA, foam sclerotherapy and surgery). Forty-nine of the participants randomised to EVLA ($n = 210$) underwent either foam sclerotherapy ($n = 46$) or surgery ($n = 3$). Of the 207 participants randomised to receive foam sclerotherapy, nine received either EVLA ($n = 6$) or surgery ($n = 3$). Of the participants randomised to surgery ($n = 213$), 17 participants underwent either EVLA ($n = 8$) or foam sclerotherapy ($n = 9$). More participants in the surgery arm received no treatment ($n = 17$) than in the foam sclerotherapy ($n = 10$) or EVLA ($n = 5$) arms.

TABLE 83 Deterministic sensitivity analysis for foam sclerotherapy vs. surgery

Intervention	Incremental cost (95% CI), £	Incremental QALYs (95% CI)	ICER (vs. surgery) (£)
Scenario 1: routine follow-up costs excluded following foam sclerotherapy and EVLA			
Surgery	–	–	–
Foam sclerotherapy	−753 (−903 to −604)	−0.006 (−0.021 to 0.009)	127,682
Scenario 2: analysis based on participants with unilateral disease only			
Surgery	–	–	–
Foam sclerotherapy	−553 (−694 to −412)	−0.006 (−0.031 to 0.020)	99,867
Scenario 3: analysis based on participants with unilateral disease and only GSV involvement			
Surgery	–	–	–
Foam sclerotherapy	−561 (−722 to −400)	−0.018 (−0.044 to 0.009)	31,771
Scenario 4: analysis based on QALYs derived from the SF-6D			
Surgery	–	–	–
Foam sclerotherapy	−602 (−740 to −464)	−0.001 (−0.013 to 0.011)	478,055
Scenario 5: analysis based on full multiple imputation data sets			
Surgery	–	–	–
Foam sclerotherapy	−553 (−676 to −430)	−0.009 (−0.024 to 0.007)	64,600
Scenario 6: analysis based on multiple imputation data sets with participants receiving no treatment and follow-up dropped			
Surgery	–	–	–
Foam sclerotherapy	−581 (−721 to −441)	−0.008 (−0.023 to 0.006)	68,901

TABLE 84 Treatment costs by treatment allocation group

Treatment details	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	210			207			213		
Treatment received									
Presented for EVLA (*n*, %)	203	96.7		6	2.9		8	3.8	
Presented for foam (*n*, %)	46	21.9		191	92.3		9	4.23	
Number of foam treatments (*n*, mean, SD)	46	1.07	0.25	191	1.15	0.39	9	1.00	0.00
Presented for surgery (*n*, %)	3	1.4		3	1.5		183	85.9	
No recorded treatment (*n*, %)	5	2.4		10	4.8		17	8.0	
Treatment durations[a]									
Cumulative procedure time (minutes)									
EVLA (*n*, mean, SD)	194	59.41	28.48	204	0.86	7.11	212	1.63	9.17
Foam sclerotherapy (*n*, mean, SD)	197	4.41	11.50	185	29.34	18.08	212	0.89	4.72
Surgery (*n*, mean, SD)	209	0.69	7.08	207	1.07	8.95	197	62.60	34.06
Treatment costs									
Staff procedure costs									
EVLA (*n*, mean, SD)	194	£326	£154	204	£5	£43	212	£10	£58
Foam sclerotherapy (*n*, mean, SD)	197	£19	£52	185	£137	£91	212	£4	£20
Surgery (*n*, mean, SD)	209	£6	£64	207	£10	£88	197	£615	£362
Recovery time costs (*n*, mean, SD)	209	£32	£10	207	£4	£11	198	£74	£37
Consumable costs (*n*, mean, SD)	210	£322	£58	207	£50	£60	213	£150	£58
Theatre use (*n*, mean, SD)	193	£31	£96	185	£14	£46	196	£231	£122
Equipment costs (*n*, mean, SD)	210	£11	£4	207	£10	£4	213	£4	£2
Preparation costs (*n*, mean, SD)	210	£29	£12	207	£28	£12	213	£29	£9
Total treatment costs									
EVLA (*n*, mean, SD)	194	£699	£195	204	£11	£90	212	£23	£126
Foam sclerotherapy (*n*, mean, SD)	197	£33	£79	185	£214	£111	212	£6	£33
Surgery (*n*, mean, SD)	209	£9	£94	207	£14	£121	197	£876	£457
Total staff procedure costs (*n*, mean, SD)	183	£349	£163	182	£157	£118	195	£637	£340
Total treatment costs[b] (*n*, mean, SD)	183	£737	£204	182	£245	£161	195	£916	£412

a Treatment duration times are the mean times of all patients randomised to the treatment strategy.
b Total treatment costs exclude the additional cost for use of theatre.

The cumulative mean time spent in treatment (see *Table 84*) was again considerably lower for those participants randomised to foam sclerotherapy than it was for those randomised to surgery. Participants randomised to EVLA spent slightly less time in treatment than those randomised to surgery. It should be noted that the small difference in time spent in treatment between EVLA and surgery (based on intention to treat) was influenced by the fact that a higher proportion of participants in the surgery arm received treatment other than that to which they had been allocated, or no treatment. The mean time from entering to leaving the treatment room was similar for EVLA (59.41 minutes) and surgery (62.60 minutes). The cumulative duration of time spent receiving foam sclerotherapy was considerably lower (29.34 minutes). Based on the treatment duration estimates, coupled with information on the numbers and grades of staff present at each procedure, the estimated staff procedure costs were £326, £137 and £615 for participants randomised to EVLA, foam sclerotherapy and surgery respectively.

Recovery time costs were highest, as expected, for participants randomised to surgery. Consumables were considerably higher in the EVLA group, on account of the high cost of the laser fibre (unit cost £256). Additional costs for the use of theatre were higher in the surgery arm, whereas equipment and preparation costs were generally similar across the EVLA, foam sclerotherapy and surgery groups.

As in the comparison of foam sclerotherapy versus surgery, in this analysis the treatment cost data showed foam sclerotherapy to be the least costly treatment option. Total treatment costs, inclusive of staff costs, consumables, equipment use, clinic/theatre preparation and recovery time costs, were £737, £245 and £916 for participants randomised to EVLA, foam sclerotherapy and surgery respectively.

Table 85 shows the follow-up resource use and cost data up to 6 months post treatment. Numbers of reported GP and other health professional consultations were slightly higher in the surgery group than in the EVLA and foam sclerotherapy groups; they were similar in each of these two groups. Attendance for the 6-week and 6-month assessments were > 80% in all treatment allocation groups. Numbers of unplanned outpatient appointments were similar among the three groups. No hospital admissions were reported in either the EVLA or the foam sclerotherapy group, and only a low number were observed in the surgery arm.

Table 86 shows the mean total NHS costs by treatment allocation group to 6-months' follow-up. As expected, total mean NHS costs (excluding additional operating theatre costs) were considerably higher in the surgery arm (£1113), with foam sclerotherapy being the least costly (£453), followed by EVLA (£951). A similar ranking was evident when additional theatre costs were included, with the difference in cost between surgery and EVLA and foam sclerotherapy increasing substantially.

Health outcomes: European Quality of Life-5 Dimensions and Short Form questionnaire-6 Dimensions

The EQ-5D and SF-6D scores are presented by treatment allocation group and time point in *Table 87*. An improvement in HRQoL was observed between baseline and 6 weeks in all treatment allocation groups (the increase being more pronounced in the EVLA-treated group in particular). A further increase in HRQoL was evident in all three treatment arms between 6 weeks and 6 months. However, the largest increase during this time interval occurred in participants allocated to foam sclerotherapy. Overall, the mean unadjusted QALYs accrued over 6 months were highest in the EVLA group.

TABLE 85 Follow-up resource use and costs by treatment allocation group

Post-treatment care costs	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	210			207			213		
Primary care									
GP consultations (*n*, mean, SD)	170	0.36	0.94	168	0.33	0.69	156	0.57	1.28
Other health professional consultations (*n*, mean, SD)	170	0.18	0.58	168	0.35	2.30	156	0.42	1.10
Total cost of GP consultations (*n*, mean, SD)	170	£14	£40	168	£11	£24	156	£20	£45
Total cost of consultations with other health professionals (*n*, mean, SD)	170	£2	£8	168	£5	£35	156	£6	£16
Total primary care costs (*n*, mean, SD)	170	£16	£43	168	£16	£42	156	£26	£47
Secondary care (planned)									
Attendance at 6-week assessment[a] (*n*, mean, SD)	192	184	95.8	189	184	97.4	180	172	95.6
Attendance at 6-month assessment[b] (*n*, mean, SD)	182	164	90	177	160	90.4	166	154	92.8
6-week assessment cost[a] (*n*, mean, SD)	192	£169	£35	189	£172	£28	180	£168	£36
6-month assessment cost[b] (*n*, mean, SD)	182	£159	£53	177	£159	£52	165	£163	£46
Secondary care (unplanned)									
Unplanned medical/surgical outpatient appointments (*n*, mean, SD)	210	0.30	0.77	207	0.24	1.29	213	0.24	0.86
Cost of unplanned outpatient appointments (*n*, mean, SD)	210	£39	£97	207	£31	£149	213	£34	£103
Admissions (*n*, mean, SD)	199	0	0	195	0	0	183	0.02	0.15
Admission costs (*n*, mean, SD)	199	£0	£0	195	£0	£0	183	£7	£49

a One follow-up attendance is retained as a cost following EVLA and foam sclerotherapy in the economic analysis.
b Research costs removed from the economic analysis.

TABLE 86 Total NHS costs by treatment allocation group

NHS costs	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	210			207			213		
Total NHS costs (excluding all theatre costs) (*n*, mean, SD)	142	£951	£179	144	£453	£225	141	£1113	£332
Total NHS costs (including theatre costs) (*n*, mean, SD)	142	£975	£205	144	£465	£239	141	£1367	£404

TABLE 87 Health state utilities by treatment allocation group

QoL measure	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Number randomised	210			207			213		
EQ-5D									
Baseline (*n*, mean, SD)	206	0.792	0.169	202	0.793	0.187	207	0.777	0.184
6 weeks (*n*, mean, SD)	184	0.894	0.145	181	0.853	0.172	164	0.864	0.180
6 months (*n*, mean, SD)	172	0.903	0.171	167	0.884	0.192	151	0.872	0.212
Total QALYs (*n*, mean, SD)	155	0.443	0.071	159	0.431	0.078	139	0.426	0.086
SF-6D									
Baseline (*n*, mean, SD)	201	0.759	0.121	197	0.760	0.125	198	0.752	0.131
6 weeks (*n*, mean, SD)	176	0.793	0.114	179	0.771	0.123	159	0.758	0.120
6 months (*n*, mean, SD)	165	0.821	0.112	164	0.802	0.127	146	0.794	0.133
Total QALYs (*n*, mean, SD)	139	0.402	0.048	151	0.391	0.056	122	0.387	0.054

Incremental cost-effectiveness: primary analysis

Based on an adjusted regression analysis of participants with complete cost and QALY data ($n = 389$), EVLA was found to produce a small (non-significant) increase in QALYs over both surgery and foam sclerotherapy at 6 months. In comparison with surgery, foam sclerotherapy had an ICER of £103,633 per QALY lost at 6 months, whereas EVLA was found to be 'dominant', that is, less costly and marginally more effective (*Table 88*). The ICER for EVLA versus foam sclerotherapy was £26,107 per QALY gained (EVLA was more costly and more effective than foam sclerotherapy). Therefore, applying a ceiling WTP threshold of £20,000, foam sclerotherapy was the favourable option from a cost-effectiveness perspective, accruing more NMB at the 6-month time frame.

The joint distribution of the incremental costs and effects for EVLA and foam sclerotherapy versus surgery, obtained from the bootstrap replicates of the analysis models, are plotted in *Figure 8*. Based on the analysis of complete case data, the majority of the points for EVLA fall below zero on the cost axis (i.e. cost saving) and above zero on the QALYs axis (increased QALYs), indicating a high probability of EVLA being both less costly and more effective than surgery.

To characterise the uncertainty surrounding the cost-effectiveness estimates, a CEAC (*Figure 9*) was derived from the bootstrapped estimates of mean incremental costs and effects. At a ceiling WTP threshold of £20,000 per QALY, foam sclerotherapy has a 78.9% chance of being cost-effective, followed by EVLA (20.9%) and surgery (0.2%). However, at a WTP threshold of ≈ £25,000, the CEACs for EVLA and foam sclerotherapy cross, and EVLA has the highest probability of being the optimal strategy on grounds of cost-effectiveness. Applying a ceiling WTP threshold of £30,000 per QALY, EVLA has a 59.4% probability of

TABLE 88 Incremental cost-effectiveness based on complete case data

Intervention	Incremental cost (95% CI), £	Incremental QALYs (95% CI)	ICER (vs. surgery) (£)	ICER (EVLA vs. foam sclerotherapy) (£)	NMB ranking at Rc £20,000
Surgery ($n = 122$)	–	–	–	–	3
Foam sclerotherapy ($n = 129$)	−662 (−826 to −498)	−0.006 (−0.030 to 0.017)	103,633	–	1
EVLA ($n = 134$)	−156 (−316 to 4)	0.013 (−0.003 to 0.029)	Dominant	26,107	2

Rc, ceiling ratio.

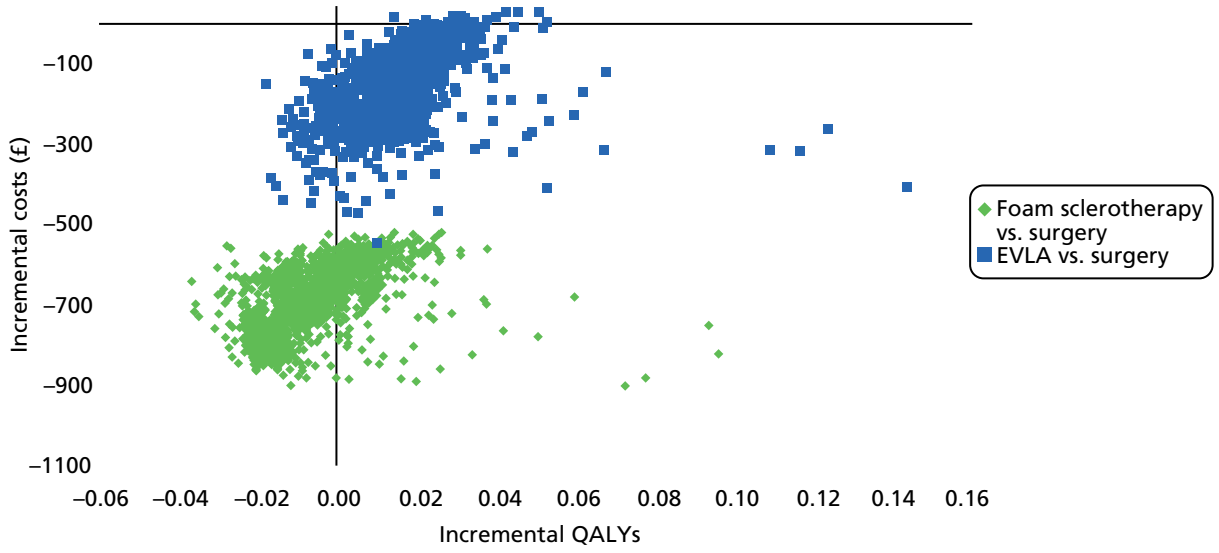

FIGURE 8 Incremental cost-effectiveness scatterplot for EVLA and foam sclerotherapy vs. surgery at 6 months.

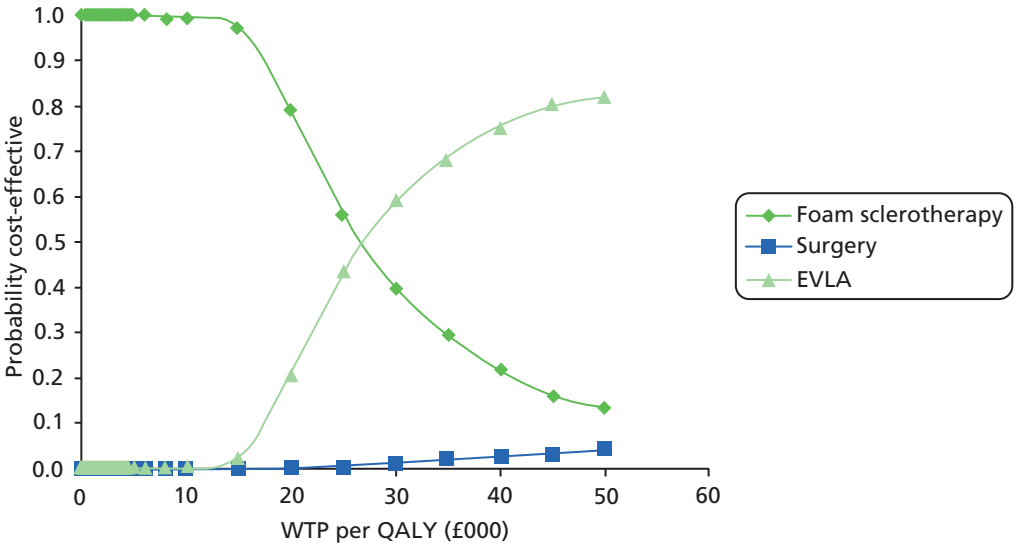

FIGURE 9 Cost-effectiveness acceptability curves for EVLA, foam sclerotherapy and surgery at 6 months.

being cost-effective. To assess the impact on these findings of missing data, multiple imputations were conducted.

Incremental cost-effectiveness: secondary analysis including additional costs for use of theatre

Applying the additional cost for the use of an operating theatre results in an increase to the reported incremental cost savings associated with EVLA and foam sclerotherapy (*Table 89*). A greater cost saved per QALY lost is evident for foam sclerotherapy versus surgery. The addition of extra theatre costs has very little impact on the ICER for EVLA versus foam sclerotherapy, and the NMB rankings remain the same.

The joint distribution of the incremental costs and effects are shown for EVLA and foam sclerotherapy versus surgery in *Figure 10*. These follow a similar pattern to those reported for the primary analysis, although the clusters fall further below zero on the cost axis (i.e. greater incremental cost saving). The surgical group retains a very low probability of being cost-effective (*Figure 11*) across all feasible ceiling WTP ratios, and at £20,000 foam sclerotherapy has an 81.4% probability of being cost-effective. The CEACs for EVLA and foam sclerotherapy begin to converge at ≈ £15,000 and again cross at a WTP threshold of ≈ £25,000 per QALY gained.

TABLE 89 Incremental cost-effectiveness with inclusion of additional theatre costs, based on complete case data

Intervention	Incremental cost (95% CI), £	Incremental QALYs (95% CI)	ICER (vs. surgery) (£)	ICER (EVLA vs. foam sclerotherapy) (£)	NMB ranking at Rc £20,000
Surgery ($n = 122$)	–	–	–	–	3
Foam sclerotherapy ($n = 129$)	−911 (−1104 to −718)	−0.006 (−0.030 to 0.017)	142,649	–	1
EVLA ($n = 134$)	−395 (−591 to −200)	0.013 (−0.003 to 0.029)	Dominant	26,625	2

Rc, ceiling ratio.

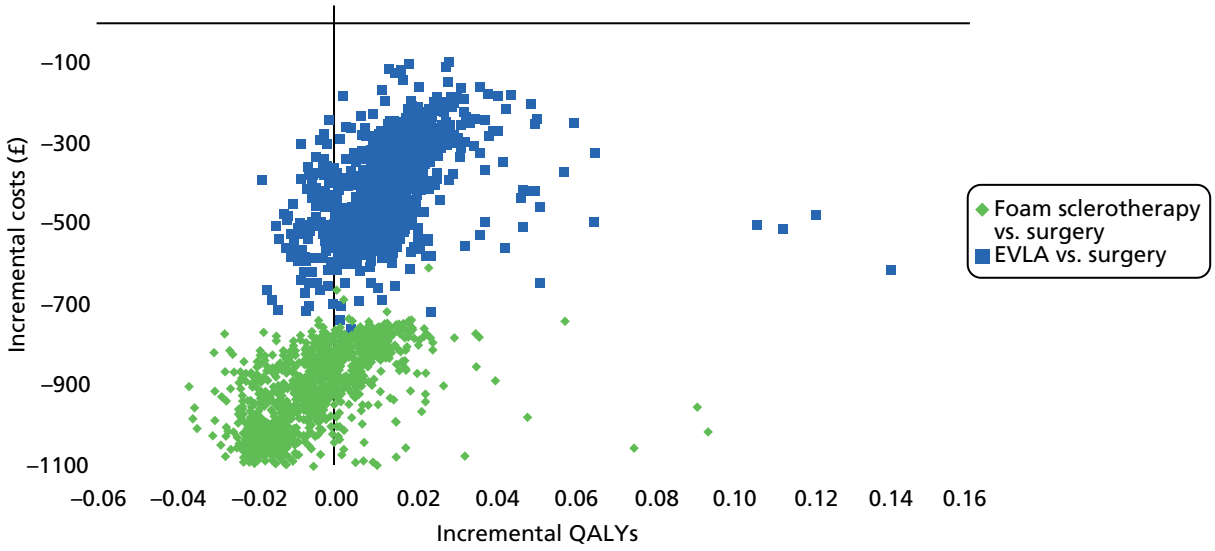

FIGURE 10 Incremental cost-effectiveness scatterplot for EVLA and foam sclerotherapy vs. surgery, including additional theatre use costs at 6 months.

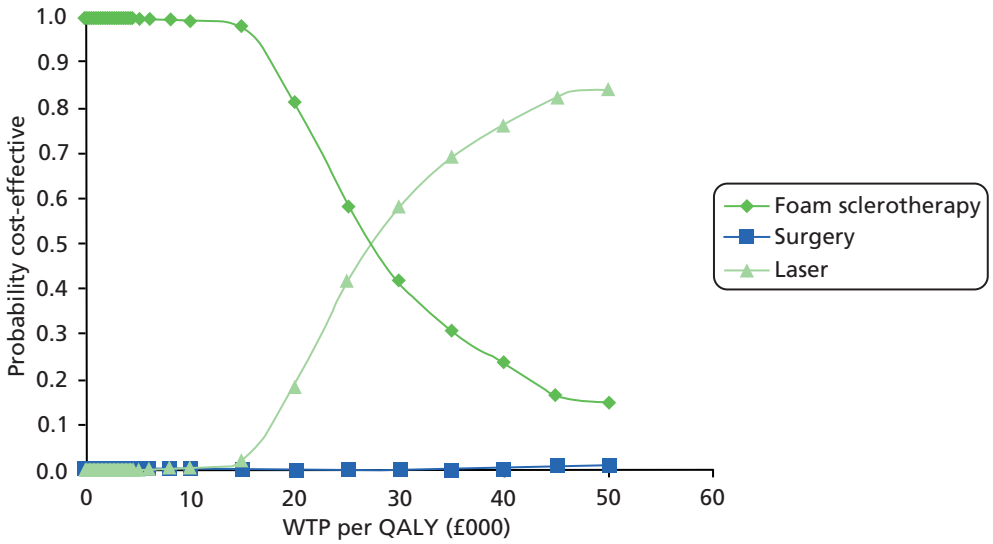

FIGURE 11 Cost-effectiveness acceptability curves for EVLA, foam sclerotherapy and surgery, including additional theatre use costs at 6 months.

Deterministic sensitivity analysis

The sensitivity analyses conducted (*Table 90*) demonstrate that foam sclerotherapy appears more cost-effective under several scenarios: specifically, when the routine follow-up cost is excluded (scenario 1), the cost per laser generator usage is incorporated (scenario 3) or QALYs are calculated from the SF-6D (scenario 6). The base-case results also appear robust to the missing data with similar results, favouring foam sclerotherapy, obtained using multiple imputation to replace missing cost and EQ-5D values (scenarios 7 and 8). However, the cost-effectiveness of EVLA versus foam sclerotherapy did improve substantially under certain scenarios. By applying the same staff profile for EVLA as for foam sclerotherapy, EVLA appears the favourable option, with an ICER of £17,146 per QALY gained. Under this scenario (scenario 2), there is a greater cost saving estimate for EVLA versus surgery. The ICER for EVLA versus foam sclerotherapy also falls below the £20,000 threshold when the analysis is restricted to subgroups (i.e. those with unilateral disease only and participants with unilateral and GSV involvement only).

The overall conclusions drawn from the base-case analysis again remain robust to several of the sensitivity analyses presented. EVLA could offer a cost-effective alternative if the treatment is performed with a similar staff profile to foam sclerotherapy. The subgroup analyses results also suggest that EVLA continues to dominate surgery, and has a favourable ICER when compared with foam sclerotherapy.

Costs directly incurred by participants and indirect costs

A further analysis was conducted incorporating both participant and indirect costs into the analysis. Participant costs comprised three main elements: self-purchased health care; travel costs for making a return visit(s) to NHS health care; and time costs of travelling and attending NHS health care. Indirect costs were defined as the production losses resulting from treatment when the participant was unable to return to normal activity. The cost of days lost was estimated using the same unit costs applied to participant time. These were calculated as outlined above (see *Methods*). Where a participant's own reported costs associated with a specific type of health service visit were missing, the mean cost by centre for that type of visit was applied.

Foam sclerotherapy versus surgery

Table 91 illustrates the mean indirect and participant costs of attending GP and outpatient appointments and also hospital admissions over the follow-up period. Mean indirect costs for foam sclerotherapy and surgery were £420 and £989 respectively. The costs associated with attending GP appointments were similar between groups, whereas the cost of attending outpatient appointments was somewhat higher in the foam sclerotherapy group. This was due to the assumption that participants would routinely attend a follow-up outpatient assessment appointment after foam sclerotherapy, but would not do so after surgery. The surgery participants incurred a higher mean cost in terms of hospital admissions, but this cost was very small owing to the low number of additional admissions (related to varicose veins treatment) which occurred during the follow-up period. Combining the indirect and participant costs with the total NHS costs has very little impact on the overall findings (*Table 92*).

To explore the uncertainty surrounding the cost-effectiveness estimate, a CEAC was derived from the results of 1000 bootstrapped replicates of mean incremental costs and effects. *Figure 12* illustrates that foam sclerotherapy has a 100% probability of being the preferred option from a cost-effectiveness perspective at 6 months.

TABLE 90 Deterministic sensitivity analysis

Intervention	Incremental cost (95% CI), £	Incremental QALYs (95% CI)	ICER (vs. surgery) (£)	ICER (EVLA vs. foam sclerotherapy) (£)	NMB ranking at Rc £20,000
Scenario 1: routine follow-up costs excluded following foam sclerotherapy and EVLA					
Surgery	–	–	–	–	3
Foam sclerotherapy	−805 (−998 to −612)	−0.006 (−0.030 to 0.017)	126,056	–	1
EVLA	−292 (−477 to −107)	0.013 (−0.003 to 0.029)	Dominant	26,494	2
Scenario 2: EVLA performed with same staff profile as foam sclerotherapy					
Surgery	–	–	–	–	3
Foam sclerotherapy	−658 (−828 to −488)	−0.006 (−0.030 to 0.017)	103,058	–	2
EVLA	−326 (−424 to −228)	0.013 (−0.003 to 0.029)	Dominant	17,146	1
Scenario 3: cost of laser machine usage incorporated					
Surgery	–	–	–	–	3
Foam sclerotherapy	−662 (−826 to −499)	−0.006 (−0.030 to 0.017)	103,713	–	1
EVLA	−123 (−282 to 37)	0.013 (−0.003 to 0.029)	Dominant	27,865	2
Scenario 4: analysis based on participants with unilateral disease only					
Surgery	–	–	–	–	3
Foam sclerotherapy	−614 (−776 to −451)	−0.009 (−0.048 to 0.030)	67,780	–	2
EVLA	−105 (−271 to 61)	0.019 (0.001 to 0.036)	Dominant	18,402	1
Scenario 5: analysis based on participants with unilateral disease and only GSV involvement					
Surgery	–	–	–	–	3
Foam sclerotherapy	−623 (−797 to −448)	−0.020 (−0.058 to 0.018)	31,300	–	2
EVLA	−114 (−281 to 53)	0.011 (−0.005 to 0.027)	Dominant	16,422	1
Scenario 6: analysis based on QALYs derived from the SF-6D					
Surgery	–	–	–	–	3
Foam sclerotherapy	−662 (−826 to −498)	−0.002 (−0.020 to 0.016)	340,775	–	1
EVLA	−156 (−316 to 4)	0.012 (−0.001 to 0.026)	Dominant	35,920	2
Scenario 7: analysis based on full multiple imputation data sets					
Surgery	–	–	–	–	3
Foam sclerotherapy	−585 (−730 to −440)	−0.010 (−0.031 to 0.010)	56,217	–	1
EVLA	−103 (−255 to 47)	0.007 (−0.008 to 0.021)	Dominant	31,589	2
Scenario 8: analysis based on multiple imputation data sets with participants receiving no treatment and follow-up dropped					
Surgery	–	–	–	–	3
Foam sclerotherapy	−621 (−782 to −459)	−0.009 (−0.030 to 0.011)	65,523	–	1
EVLA	−126 (−281 to 28)	0.007 (−0.007 to 0.021)	Dominant	30,723	2

Rc, ceiling ratio.

TABLE 91 Individual participant costs: foam sclerotherapy vs. surgery

Costs	Foam sclerotherapy			Surgery		
Number of participants	286			289		
Indirect costs (*n*, mean, SD)	223	£420	£554	220	£989	£788
Participant GP cost (*n*, mean, SD)	234	£4	£18	213	£4	£13
Participant outpatient cost (*n*, mean, SD)	286	£17	£53	289	£4	£13
Participant hospital cost (*n*, mean, SD)	272	£0	£0	254	£1	£5
Total participant cost (*n*, mean, SD)	232	£22	£63	210	£9	£21
Total costs primary analysis						
Total participant, NHS and indirect costs (*n*, mean, SD)	180	£895	£611	175	£2053	£889

TABLE 92 Incremental cost-effectiveness, including NHS, indirect and participant costs: foam sclerotherapy vs. surgery

Intervention	Incremental costs (95% CI), £	Incremental QALYs (95% CI)	ICER (£)
Surgery	–	–	–
Foam sclerotherapy	−1173 (−1371 to −974)	−0.006 (−0.021 to 0.009)	198,802

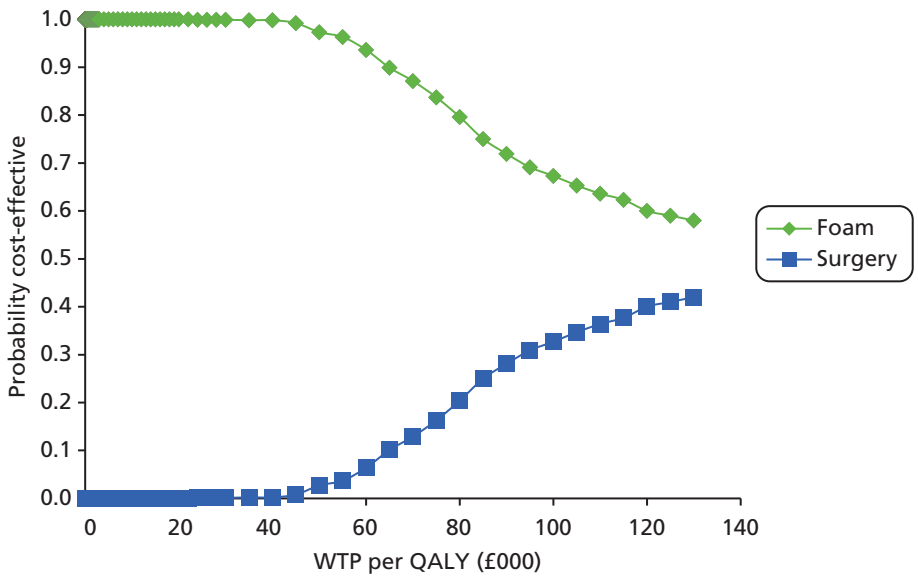

FIGURE 12 Cost-effectiveness acceptability curves, including NHS, indirect and participant costs: foam sclerotherapy vs. surgery.

Endovenous laser ablation versus foam sclerotherapy versus surgery

Table 93 documents the mean indirect and participant costs associated with use of health services over the follow-up period. The surgery treatment strategy incurred the highest mean indirect costs (£1075), followed by EVLA (£628) and foam sclerotherapy (£466). Mean participant costs of attending GP appointments were slightly higher in the surgery group, whereas higher costs of attending outpatient appointments were observed in the EVLA and foam sclerotherapy groups; again, this was due to the assumed need to attend a routine assessment appointment following these treatment modalities. As for the analysis of foam sclerotherapy versus surgery, combining the mean indirect and mean participant costs with NHS costs had very little impact on the incremental cost-effectiveness findings in this analysis (*Table 94*).

To characterise the uncertainty surrounding the cost-effectiveness estimates, a CEAC was derived (*Figure 13*). At a ceiling WTP threshold of £20,000 per QALY, foam sclerotherapy had an 85.4% probability of being cost-effective, whereas EVLA had a 14.6% chance and surgery had a 0% probability of being the preferred option. At a WTP threshold of £30,000 per QALY, foam sclerotherapy retains the highest probability (54.5%) of being the cost-effective option, followed by EVLA (probability of 45.5%), and the probability of surgery being the preferred option does not increase. The CEACs for foam sclerotherapy and EVLA do not cross until the WTP threshold is > £30,000.

TABLE 93 Participant costs: EVLA vs. foam sclerotherapy vs. surgery

Costs	EVLA			Foam sclerotherapy			Surgery		
Number of participants	210			207			213		
Indirect costs (*n*, mean, SD)	174	£628	£653	164	£466	£597	164	£1075	£852
Participant GP cost (*n*, mean, SD)	170	£2	£7	168	£4	£21	156	£5	£15
Participant outpatient cost (*n*, mean, SD)	210	£14	£22	207	£14	£38	213	£4	£14
Participant hospital cost (*n*, mean, SD)	199	£0	£0	195	£0	£0	183	£1	£6
Total participant cost (*n*, mean, SD)	167	£17	£24	167	£19	£48	153	£11	£23
Total participant, NHS and indirect costs (*n*, mean, SD)	124	£1541	£632	127	£945	£661	129	£2196	£930

TABLE 94 Incremental cost-effectiveness, including NHS and participant costs: EVLA vs. foam sclerotherapy vs. surgery

Intervention	Incremental cost (95% CI), £	Incremental QALYs (95% CI)	ICER (vs. surgery) (£)	ICER (EVLA vs. foam sclerotherapy) (£)	NMB ranking at Rc £20,000
Surgery	–	–	–	–	3
Foam sclerotherapy	−1271 (−1459 to −1083)	−0.006 (−0.030 to 0.017)	198,977	–	1
EVLA	−660 (−849 to −471)	0.013 (−0.003 to 0.029)	Dominant	31,546	2

Rc, ceiling ratio.

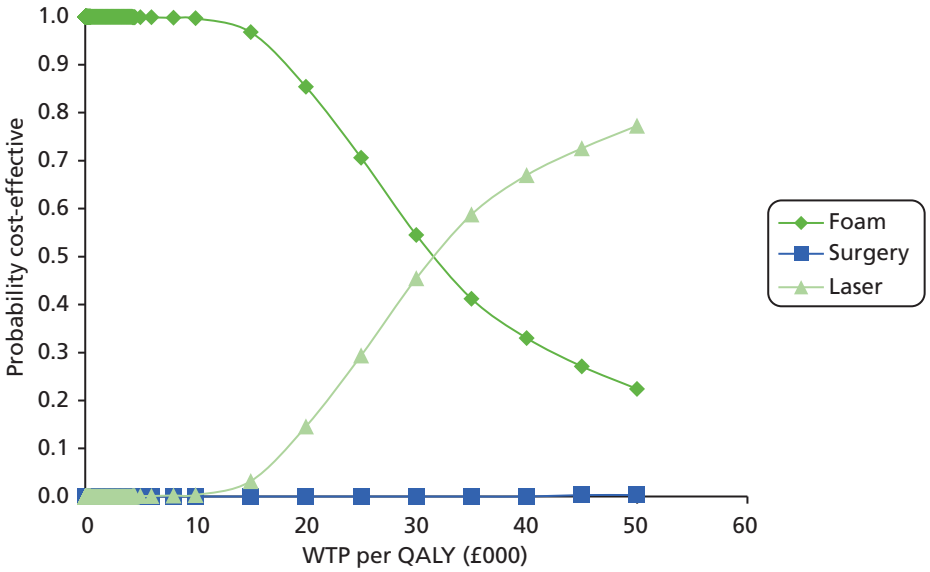

FIGURE 13 Cost-effectiveness acceptability curves, including NHS, indirect and participant costs: EVLA vs. foam sclerotherapy vs. surgery.

Discussion

Summary of key results

Based on the primary analysis of foam sclerotherapy versus surgery data, foam was found to result in a cost saving of £102,106 per QALY lost in comparison with surgery. Considering that society might be required to receive compensation of at least £20,000 for a QALY loss, this result is highly favourable for foam, suggesting good value for money for the NHS in comparison with surgery. The high value of the ICER is driven by the comparatively modest cost of foam sclerotherapy treatment. The results were robust to a range of alternative assumptions relating to unit cost estimation, restriction of the analysis to specific subgroups and multiple imputation of missing data.

For the analysis of EVLA versus foam sclerotherapy versus surgery, very similar results were obtained for the comparison between foam sclerotherapy and surgery. From the three-way comparison of data at 6-months follow-up, EVLA was found to be less costly and marginally more effective than surgery, and therefore 'dominant' (i.e. better than surgery in terms of both costs and QALYs). In the base-case analysis it was estimated that the ICER for EVLA versus foam sclerotherapy was ≈ £26,000. Therefore, adopting the same ceiling WTP ratio of £20,000 per QALY, foam sclerotherapy produced the greatest NMB at 6 months, followed by EVLA, followed by surgery. Considering the results of the probabilistic analysis, foam sclerotherapy had the greatest probability of being cost-effective (≈ 78%) at a threshold value of £20,000 per QALY, whereas EVLA had a ≈ 21% chance and surgery a < 1% chance. However, increasing the WTP threshold to £30,000, EVLA was found to have the higher probability (≈ 60%) of being the most cost-effective option.

Further, EVLA was found to generate greater NMB under certain scenarios presented in the sensitivity analysis, namely, when EVLA incorporated a similar staff profile to foam sclerotherapy (performing the procedure with the presence of a surgeon and one or two additional nurses); when the analysis was restricted to include participants with unilateral disease only; and when the analysis was based on participants with unilateral and GSV involvement only. The base-case results demonstrated that EVLA generated a cost saving of £156 compared with surgery. This cost saving increased when EVLA was assumed to adopt a similar staff profile to foam sclerotherapy (£326). However, when the cost per usage of the laser generator (assumed as loaned free of charge) was included in the EVLA treatment, the cost saving versus surgery reduced (£123).

Explanation of results

The ICER for foam sclerotherapy versus surgery in both analyses (foam sclerotherapy vs. surgery and EVLA vs. foam sclerotherapy vs. surgery) showed that foam sclerotherapy had reduced effectiveness but at a lower cost. The ICER remained robust to all scenarios presented in the sensitivity analyses. On the basis of the data presented, it would be accepted NHS practice to conclude that foam sclerotherapy would be considered the favourable option from a cost-effectiveness perspective at the 6-month time frame.

Similar results were found for foam sclerotherapy versus surgery in the three-way comparison. The ICER remained robust to all scenarios presented in the sensitivity analysis. EVLA was found to give a small increase in QALYs compared with both foam sclerotherapy and surgery. EVLA was, on average, less costly and more effective than surgery, and was thus dominant. However, the ICER for EVLA versus foam sclerotherapy showed that although it produced higher QALYs, it did so at an increased cost. The ICER for EVLA versus foam sclerotherapy in the base-case analysis was higher than the accepted threshold, and for this reason foam sclerotherapy remains the preferred option from a cost-effectiveness perspective at 6 months.

Strengths and limitations

One of the key strengths of this study was the multicentre RCT design, which comprised 11 centres around the UK, adding to the applicability of results more widely. The inclusion of a comprehensive cost-effectiveness analysis, based on best practice guidelines, within a RCT is another key strength. A detailed micro-costing method was implemented, ensuring that variations in treatment strategy costs across participating centres were accurately reflected in the analysis. To ensure that results were robust to the primary outcome measure (EQ-5D), QALYs were also estimated using responses from the SF-36 (converted into the SF-6D).

Some data were missing for cost and QALY outcomes. However, multiple imputation of missing resource use, cost and EQ-5D data did not alter the conclusions of the analysis. It should be noted that the results of the trial-based cost-effectiveness analysis pertain only to a short period of follow-up (6 months). Therefore, any differences across treatment arms in terms of recurrence over the longer term, and the associated cost and QALY implications, were not addressed in this phase of the study. For this reason, we developed an economic model (see *Chapter 10*) to extrapolate results from the 6-month trial-based analysis over a longer time horizon. In addition, further data will be collected from participants after 5 years.

Summary/conclusions

To summarise, within the trial period it was found that foam sclerotherapy had the highest probability of being the most cost-effective option under base-case assumptions. These results remained robust under all scenarios presented in the sensitivity analysis for foam sclerotherapy versus surgery. However, our analysis shows that under certain circumstances in the three-arm analysis (EVLA vs. foam sclerotherapy vs. surgery), EVLA may generate the greatest NMB in comparison with foam sclerotherapy and surgery. Data from the subgroup analyses would suggest that EVLA is more likely to be cost-effective in the subgroup of participants treated for unilateral GSV involvement only. Further, if EVLA could be performed using a similar staff profile to foam sclerotherapy, it may offer a cost-effective approach to treatment.

Although these results provide useful information on the short-term costs and effects of the different procedures, they are not sufficient for determining the optimal approach to treatment over a longer time horizon. This is because any differential effects of the treatments on costs and outcomes may persist far into the future. In addition, the risk of clinical recurrence beyond 6 months may be found to differ significantly between the alternative treatment strategies, altering the cost-effectiveness rankings of treatments in the long term. Therefore, *Chapter 10* reports on the findings of a decision modelling exercise, designed to extrapolate these cost-effectiveness findings over extended time horizons. Extended follow-up of the CLASS cohort to 5 years will provide a means of validating this modelling exercise in the future.

Chapter 10 Cost-effectiveness modelling

Introduction

The aim of this chapter is to assess the cost-effectiveness of the alternative treatment modalities for varicose veins over the longer term. The within-trial analysis provides useful information on the short-term costs and effects of the alternative interventions, but it is important to discover whether or not the effects of treatment on outcomes persist into the future. This is because recurrence of varicose veins in the long term after any particular treatment will lead to reductions in QoL and further costs. In order to address this issue, additional information was gained through modelling expected future costs and outcomes over longer time horizons (through to 5 and 10 years). The specific objectives of this chapter are to:

- describe the development of a model to extrapolate the costs and consequences of surgery, foam sclerotherapy and EVLA treatments over extended time horizons of 5 and 10 years
- compare the treatment modalities incrementally in terms of costs and QALYs, using the NMB framework to identify the optimal strategy.

Methods

General structure of the model

A cost-effectiveness Markov model was developed using TreeAge Pro 2012, R2.1 (TreeAge Software, Inc., Williamstown, MA, USA). The model was based on care pathways developed in consultation with clinical members of the team, describing the possible temporal sequences of events that patients may experience following their initial treatment. The model structure describes the logical and temporal sequence of events from the initial treatment until the patient's death.

The model was constructed to simulate transitions between discrete health states on a 6-month time interval (Markov cycle). For the first 6-month cycle, model data were taken directly from CLASS trial data. Beyond 6 months, the best available evidence on the risk of recurrence following initial treatment with the alternative treatment modalities was used to model subsequent costs and consequences over an extended time horizon. The model was designed to inform the optimal approach to treatment in patients considered clinically suitable for all three surgical procedures (as was the case for all patients randomised in the CLASS trial). It simultaneously compared the three treatment modalities, but did not include a no treatment (or conservative management) arm. As the model focused on the three-way treatment comparison, the model input parameters were based only on data from centres that randomised patients to all three procedures.

Modelled cohort

The model was analysed for a cohort of patients with mean age and sex matching those of participants recruited at CLASS trial sites which offered randomisation between all three treatment modalities. Initially, the model was populated based on cost and utility data obtained from all randomised patients, but the impact of basing model inputs on patients with unilateral disease only (and those with unilateral disease and GSV involvement only) was also assessed.

Definition of health states

For the base-case analysis, a simple model was specified using five main states: 'pre-treatment primary varicose veins', 'post-primary treatment of varicose veins' (following surgery, foam sclerotherapy or EVLA), 'clinical recurrence', 'post treatment of recurrent varicose veins' and 'death' from all causes (*Figure 14*). All patients commenced in the 'pre-treatment primary varicose veins' state, and then moved to the

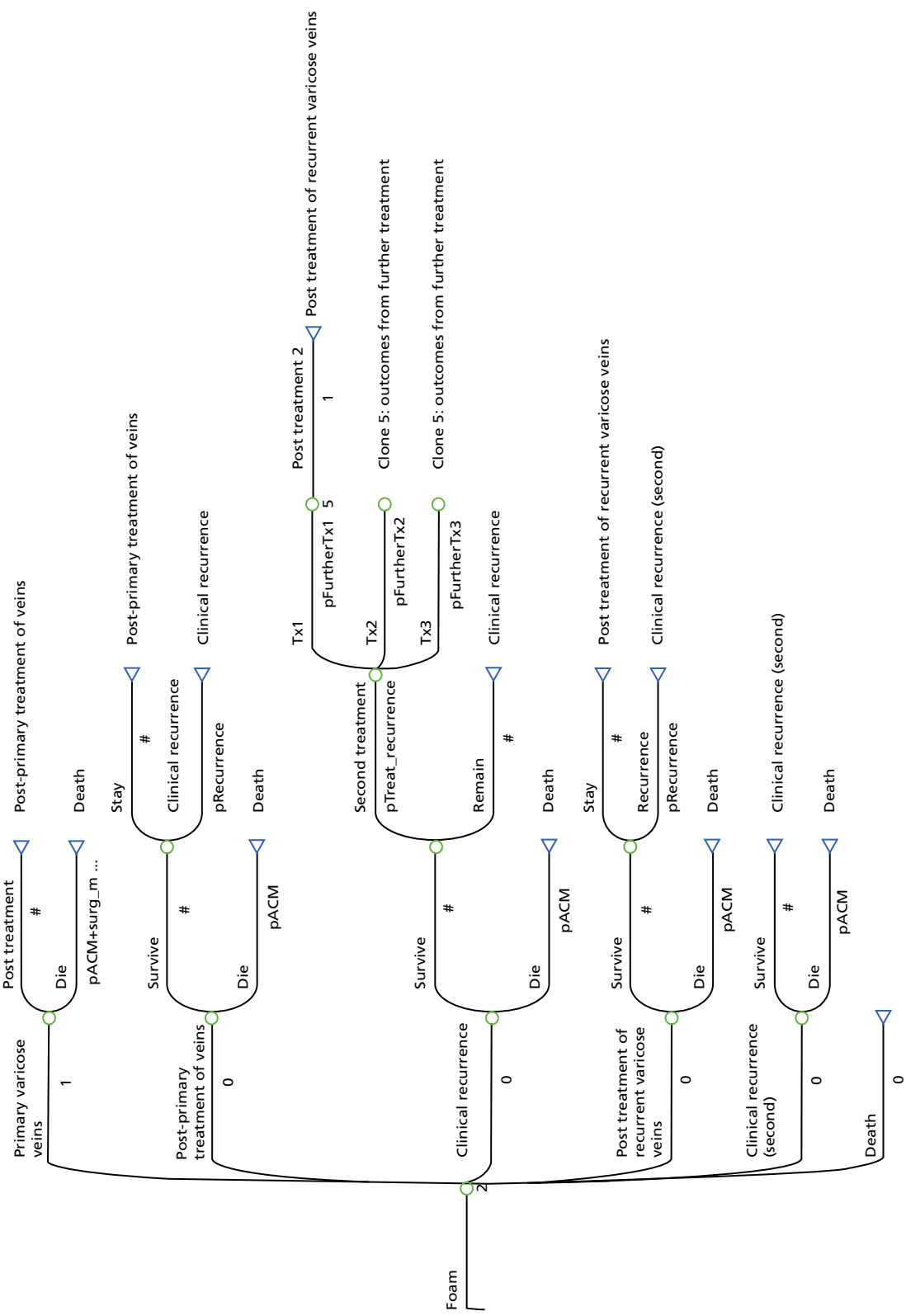

FIGURE 14 Diagram showing the model structure. pACM, probability of death from all causes; Tx1, ultrasound-guided foam sclerotherapy; Tx2, surgery; Tx3, EVLA.

corresponding post-treatment state for the start of the second model cycle. Over subsequent model cycles, a constant risk of clinical recurrence, specific to the initial treatment modality received, was applied to patients in the post-treatment states. Following clinical recurrence, patients could either present for further treatment (surgery, foam sclerotherapy or EVLA), and then transit to the 'post treatment of recurrent varicose veins' state, or they could remain in the 'clinical recurrence' state. For patients experiencing a second recurrence following secondary treatment, a simplifying assumption was made that these patients would not proceed to further treatment. The impact of allowing any number of further repeat treatments for clinical recurrence was also assessed through sensitivity analysis.

Clinical recurrence

To inform the risk of recurrence in the model, existing systematic reviews assessing the longer-term clinical effectiveness of the alternative treatment modalities for varicose veins were consulted.[28,52,56,93] The most recent of these was carried out for NICE Clinical Guideline 168 on varicose veins in the legs.[28] Within the review prepared for the NICE evaluation, the authors presented the findings of a random-effects network meta-analysis of treatment-specific probabilities of clinical recurrence over time. This analysis was based on summary data from eight RCTs that included clinical recurrence as an outcome, seven comparing surgery against endothermal treatment (including EVLA), two comparing surgery against foam sclerotherapy and one comparing foam sclerotherapy against endothermal treatment. The duration of follow-up in the majority of included studies was 12 or 24 months, although one small trial comparing surgery and endothermal treatment reported follow-up to 36 months.[94] It should be noted that the endothermal treatments (EVLA and endovenous radiofrequency ablation) were pooled for the purpose of this meta-analysis. The monthly probabilities of recurrence presented in the updated NICE guideline were applied in the model, transformed into constant 6-month probabilities (*Table 95*). Application of these probabilities yields predicted recurrence rates at 5 years of ≈ 40% for foam sclerotherapy, ≈ 37% for surgery and ≈ 29% for EVLA. It should be noted that plans are in place to assess clinical recurrence at 5 years after treatment through extended follow-up of the CLASS trial participants, but these data are not yet available. Sensitivity analysis was used to assess the impact of varying the recurrence rates on the cost-effectiveness of the alternative treatment modalities.

Utilities estimates

The utility estimate for pre-treatment primary varicose veins was taken as the mean baseline EQ-5D score across all treatment arms of the CLASS trial. For the base-case model, the utility values applied to the post-treatment states were derived by regressing the 6-month EQ-5D values on treatment group, baseline EQ-5D score and the minimisation variables (*Table 96*). The method of recycled predictions[84] was used to recover the mean estimated 6-month utility value following surgery, and the estimated mean utility increments associated with foam sclerotherapy and EVLA were applied to patients receiving these treatment modalities. Cluster robust standard errors, obtained from the regression analysis of utility data, were used to fit distributions to the incremental utility parameters for probabilistic sensitivity analysis (PSA). Further, the utility pay-off in the first model cycle was adjusted so that the QALYs generated in the first 6 months were consistent with those derived from the within-trial analysis. It was assumed that following

TABLE 95 Monthly probabilities of clinical recurrence applied in the model[28]

Treatment	Mean	Standard error	Assumed distributional form
Surgery	0.008818	0.00306	Beta
Foam sclerotherapy	0.0115	0.009929	Beta
EVLA	0.006532	0.003448	Beta

TABLE 96 European Quality of Life-5 Dimensions utility values applied in the model

State	EQ-5D utility value	Standard error	Assumed distributional form
Pre-treatment primary varicose veins	0.790	0.009	Beta
Post-treatment for primary veins (surgery)	0.884	0.0104[a]	Beta
Post-treatment utility increment (foam sclerotherapy)	–0.009	0.018[b]	Normal
Post-treatment utility increment (EVLA)	0.016	0.0121[b]	Normal
Clinical recurrence	0.790	0.009	Beta

a Cluster bootstrapped standard errors.
b Cluster robust standard errors.

clinical recurrence, patients would revert back to the pre-treatment EQ-5D utility value. This assumption is conservative in favour of treatments with higher clinical recurrence rates, because some previous evidence suggests that the utility decrement associated with recurrence might be greater than the utility increment associated with initial treatment success.[28]

Resource use and costs

The costs included in the model were derived from the analysis of patient-level cost data collected in the CLASS trial (reported in *Chapter 9*), supplemented by assumptions about further resource use associated with clinical recurrence. The model-based analysis adopted a health and social care perspective, although no social care costs were identified as being relevant to the comparison of the alternative treatment modalities.

Initial treatment costs

For the initial 6-month cycle, we employed the same general linear regression model used to analyse the CLASS patient-level cost data. However, for the purpose of populating the economic model, the analysis of cost data was not restricted to patients with complete QALY data. The approach of recycled predictions was used to recover the estimated mean cost in the surgery arm (at 6 months), adjusted for any potential imbalance in the covariates at baseline. This cost accounts for the initial treatment, any perioperative complications experienced and any subsequent resource use occurring within the first 6 months of follow-up (*Table 97*). The incremental costs associated with foam sclerotherapy and EVLA, compared with surgery (derived from the regression model), were applied to recover the expected costs for patients receiving these treatment modalities in the model.

TABLE 97 Initial treatment and 6-month follow-up costs applied in the model

Description	Initial 6-month cost (£)	Standard error (£)	Assumed distributional form
Conventional surgery	1110	80[a]	Gamma
Incremental cost (foam sclerotherapy)	–655	85[b]	Normal
Incremental cost (EVLA)	–160	83[b]	Normal

a Cluster bootstrapped standard error.
b Cluster robust standard errors.

Costs of recurrence

Assumptions were required regarding the approach to management of clinical recurrence. In the base case it was assumed that the approach to initial treatment would not determine the approach to treating clinical recurrence. Initially, the assumptions regarding the treatment of clinical recurrence were taken from the modelling exercise undertaken to inform the NICE guideline.[28] Based on consultation with the NICE Guideline Development Group (GDG), the authors of the NICE report assumed that 75% of patients experiencing a recurrence would receive further interventional treatment, and that regardless of initial treatment modality, 12% would receive surgery, 42% would receive foam and 46% would receive EVLA. For the costs of these procedures for recurrent varicose veins, we applied the same estimated 6-month mean costs as applied for the initial treatment, derived from our analysis of the directly collected trial data (see *Table 97*). However, we also assessed the impact of applying the NHS reference cost for the treatment of recurrent varicose veins[86] in a sensitivity analysis.

It was further assumed that patients receiving treatment for recurrence would spend 1 year on average in the 'clinical recurrence' state prior to receiving treatment. The impact of this assumption was assessed through sensitivity analysis. In the economic model developed for the NICE guideline, it was also assumed that patients experiencing a clinical recurrence would, on average, incur the cost of a further 2.5 GP visits (£75)[87] and subsequent assessment in an outpatient setting (£165) – including a duplex scan (£52.84)[86] – prior to treatment. To retain consistency with this previous analysis, these additional costs were also incorporated in the current model.

Complications

Although complications have the potential for significant cost and outcome implications, it was assumed that serious long-term complications would be rare and that these would not differentially affect resource use across the treatment groups. In addition, the differential impact of any short-term complications on resource use is implicitly captured in the model via application of the 6-month cost estimates obtained from the trial-based cost-effectiveness analysis (see *Chapter 9*), while the impact of any complications on health status is captured through application of the 6-month QALY and EQ-5D estimates. Therefore, resource use associated with any long-term complications, other than clinical recurrence, was not explicitly included in the model.

Mortality

Within any cycle of the model, patients also faced a risk of dying from any cause. These age- and sex-specific probabilities of death were based on UK interim life tables.[90,95]

Analysis

The model was initially run over a 5-year time horizon, which is the duration to which the CLASS study follow-up will ultimately be extended in order to provide a validity check on initial model-based estimates of cost-effectiveness. Following this, we explored the impact of extending the model time horizon to 10 years, assuming constant risks of clinical recurrence. Future costs and QALYs were discounted at a rate of 3.5% per annum in line with the NICE reference case.[96] The model-based analysis was restricted to the health and social care perspective, comparing the expected health service costs and QALYs generated by each treatment modality incrementally from the least costly to the most costly. In order to help identify the optimal approach to treatment, the NMB framework was used, where the NMB for any given strategy is equal to the accrued QALYs multiplied by the ceiling ratio (Rc) of WTP per QALY gained, minus the strategy costs.

$$\text{NMB} = (\text{QALYs} \times \text{Rc}) - \text{costs}. \quad (2)$$

To help interpret the results for decision-making, the accepted value of £20,000 was placed on the Rc of WTP per QALY,[96] and the strategy generating the greatest NMB at this value of Rc identified. In order to characterise the uncertainty surrounding selection of the optimal strategy, the model was analysed probabilistically and the mean costs and effects reported. Each input parameter in the model was assigned an appropriate distribution reflecting the uncertainty surrounding it. The probabilistic analysis proceeded by randomly selecting a value from the assigned distribution for each model parameter, and recomputing the model results. This process was repeated 10,000 times to produce an empirical estimate of the uncertainty surrounding the model-based estimates of NMB. Distributions for the incremental cost and utility parameters (for foam and EVLA vs. surgery) applied in the model were defined using the mean regression-based estimates with cluster robust standard errors (see *Tables 96* and *97*).

Deterministic sensitivity analysis

Further deterministic sensitivity analysis was undertaken to assess the robustness of the findings to various parameter and structural assumptions applied in the base-case analysis. Deterministic sensitivity analysis assessed the impact on findings of:

- applying additional overhead costs to reflect the opportunity cost of operating theatre space for procedures using this resource
- basing the model cost and utility input parameters on the estimates obtained from the trial-based multiple imputation analysis
- basing the model cost and utility input parameters on the trial-based estimates obtained for patients with unilateral disease only (to eliminate any potential bias in estimated cost-effectiveness associated with patients receiving simultaneous treatment for their contralateral leg)
- altering assumptions about the proportional distribution of patients receiving different treatment modalities (surgery, foam sclerotherapy and EVLA) for clinical recurrence
- altering assumptions about the proportion of patients with clinical recurrence who proceed to further surgical treatment
- increasing/decreasing the duration of time between clinical recurrence and subsequent treatment
- allowing patients to come back for further surgical treatment for any number of clinical recurrences, over an extended time horizon
- applying the NHS reference cost for treatment of recurrent unilateral varicose veins, rather than the bottom-up trial-based estimates of mean procedure costs
- assuming equal utility between treatment arms at 6 months
- basing utility inputs on responses to the SF-36, scored via the SF-6D.

Sensitivity to alternative structural assumptions

Given the uncertainty surrounding the estimated differences in generic HRQoL between treatment arms at 6 months, an alternative model specification was also assessed using pre- and post-treatment health states defined by clinical severity. Within this model it was assumed that changes in QoL are determined solely by transitions across the clinical severity states, and are not otherwise influenced by the treatment modality received.

Four mutually exclusive clinical states were defined based on the VCSS.[97] This instrument was chosen as the basis for defining the health states as it reports the presence of varicose veins and the severity of symptoms based on an objective clinical assessment, rather than the patients' subjective perception. It was felt desirable that the severity states in the model should reflect underlying clinical status rather than perceived status. The defined states were also found to correlate reasonably well with participants' EQ-5D scores, which reflect participants' self-reported general health status and are used for estimating QALYs within the model. The states chosen for this model are summarised in *Table 98*.

TABLE 98 Description of health states in the Markov model

State	Description
State 2: pre treatment	VCSS score 1–3 prior to treatment
State 3: pre treatment	VCSS score 4–6 prior to treatment
State 4: pre treatment	VCSS score > 6 prior to treatment
State 1: post treatment	VCSS score 0 post treatment
State 2: post treatment	VCSS score 1–3 post treatment
State 3: post treatment	VCSS score 4–6 post treatment
State 4: post treatment	VCSS score > 6 post treatment
State 2: recurrence	VCSS score 1–3 post recurrence
State 3: recurrence	VCSS score 4–6 post recurrence
State 4: recurrence	VCSS score > 6 post recurrence
Dead	Death from all causes

Figure 15 provides a diagram of this alternative model structure. The modelled cohort was initially spread across the pre-treatment states 2–4, reflecting the fact that all participants in the CLASS trial had varicose veins at baseline. Probabilities of transition to the alternative post-treatment states were derived using a multivariate ordinal logistic regression model. The ordinal post-treatment VCSS state at 6 months was regressed on treatment allocation group, pre-treatment VCSS state and the minimisation factors [age group, sex, vein involvement (GSV/SSV/both) and laterality (unilateral/bilateral)]. This model predicts the probability of transition to each of the clinical severity states at 6 months, based on treatment allocation group adjusted for baseline disease status and the minimisation covariates. These treatment-specific predicted probabilities of moving to the alternative post-treatment severity states were applied in the decision model.

The utility value for each model state was taken as the estimated mean EQ-5D index score for patients in that state (*Table 99*). In this structural specification, no adjustments were made to the mean state utility values by treatment allocation group. This modelling assumption constrains the modelled QALYs to be influenced only by the impact of the alternative treatments on the probabilities of transition to the different clinical health states following treatment, as well as the risk of recurrence over time. A further assumption applied in this model was that clinical recurrence results in the patient moving down one clinical severity state (apart from those patients already in state 4 following initial treatment), taking the EQ-5D utility value back to the pre-treatment level for that state. This alternative model was analysed in the same way as described above, using 10,000 probabilistic iterations.

Results

Base-case analysis

Table 100 presents the findings of the base-case modelling exercise over a 5-year time horizon. Mean costs and effects are reported based on 10,000 probabilistic iterations of the model. The findings indicate increased costs and QALYs associated with EVLA in comparison with foam sclerotherapy. The incremental cost per QALY gained (EVLA vs. foam) is below the accepted Rc of £20,000. Surgery is associated with increased costs compared with EVLA, but on average produces slightly fewer QALYs over 5 years. This is driven by the slightly lower number of QALYs observed for surgery at 6-months follow-up, a slightly lower EQ-5D score applied at 6 months and beyond, and a slightly higher clinical recurrence rate applied to

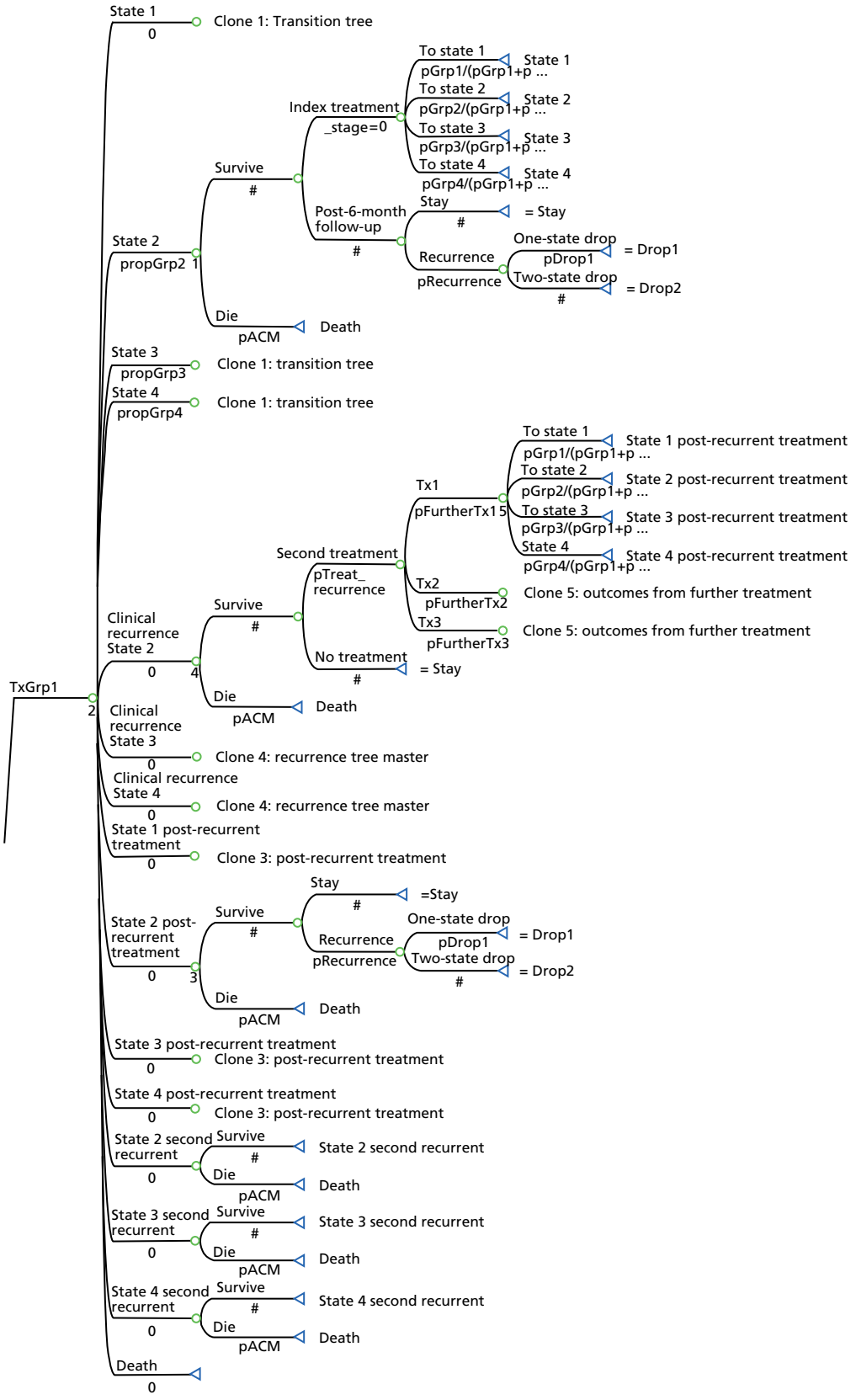

FIGURE 15 Diagram showing the alternative model structure. Drop 1, drop 1 severity state; Drop 2, drop 2 severity states; pACM, probability of death from all causes; pGrp1, probability of moving to clinical severity state 1 following treatment; pGrp2, probability of moving to clinical severity state 2 following treatment; pGrp3, probability of moving to clinical severity state 3 following treatment; pGrp4, probability of moving to clinical severity state 4 following treatment; propGrp2, proportion starting model in clinical severity state 2; propGrp3, proportion starting model in clinical severity state 3; propGrp4, proportion starting model in clinical severity state 4; Tx1, ultrasound-guided foam sclerotherapy; Tx2, surgery; Tx3, EVLA.

TABLE 99 European Quality of Life-5 Dimensions utility values applied in the model

State	EQ-5D utility value	Standard error	Distribution for PSA
State 2: pre treatment	0.809	0.0117	Beta
State 3: pre treatment	0.802	0.0083	Beta
State 4: pre treatment	0.745	0.0179	Beta
State 1: post treatment	0.940	0.0104	Beta
State 2: post treatment	0.894	0.0099	Beta
State 3: post treatment	0.799	0.0338	Beta
State 4: post treatment	0.754	0.0203	Beta
State 2: recurrence	0.809	0.0117	Beta
State 3: recurrence	0.802	0.0083	Beta
State 4: recurrence	0.745	0.0179	Beta

TABLE 100 Base-case analysis over a 5-year time horizon

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Foam sclerotherapy	664	0	4.000	0	0	0.168
EVLA	1095	431	4.119	0.118	3640	0.787
Surgery	1300	206	4.040	–0.078	Dominated	0.045

Note
Rc is ceiling ratio of WTP per QALY gained.

surgery compared with EVLA. This leads to surgery being dominated by EVLA, that is, EVLA is less costly and more effective. Applying a ceiling WTP ratio of £20,000 per QALY to help interpret the probabilistic results, EVLA had the highest probability (78.7%) of being cost-effective, with foam sclerotherapy second (16.8%) and surgery third (4.5%).

Figure 16 plots the proportion of probabilistic iterations favouring each of the alternative strategies (in terms of NMB) at increasing levels of WTP per QALY. This figure shows that as WTP increases beyond £30,000, EVLA has ≈ 80% chance of being considered the optimal strategy from a cost-effectiveness perspective.

Table 101 and *Figure 17* summarise the results when adopting a 10-year time horizon (assuming a constant risk of recurrence over time). A similar pattern of results is obtained, although the incremental cost per QALY gained for EVLA versus foam decreases to £2065. There is also slightly more uncertainty over the optimal treatment modality when adopting the 10-year time horizon (see *Figure 17*), but EVLA retains the highest chance (76%) of being cost-effective at a ceiling ratio of £20,000 per QALY.

Deterministic sensitivity analysis

Table 102 demonstrates the sensitivity of the base-case modelling results to uncertainty surrounding several key input parameters and modelling assumptions. In general, the findings are robust to most changes. However, the ordering of strategies does partially switch when using the full multiple imputation data set to inform the cost and utility parameters of the model (see scenario 2 in *Table 102*). Under this scenario, the mean increased cost of surgery in relation to foam and EVLA drops somewhat, owing to a

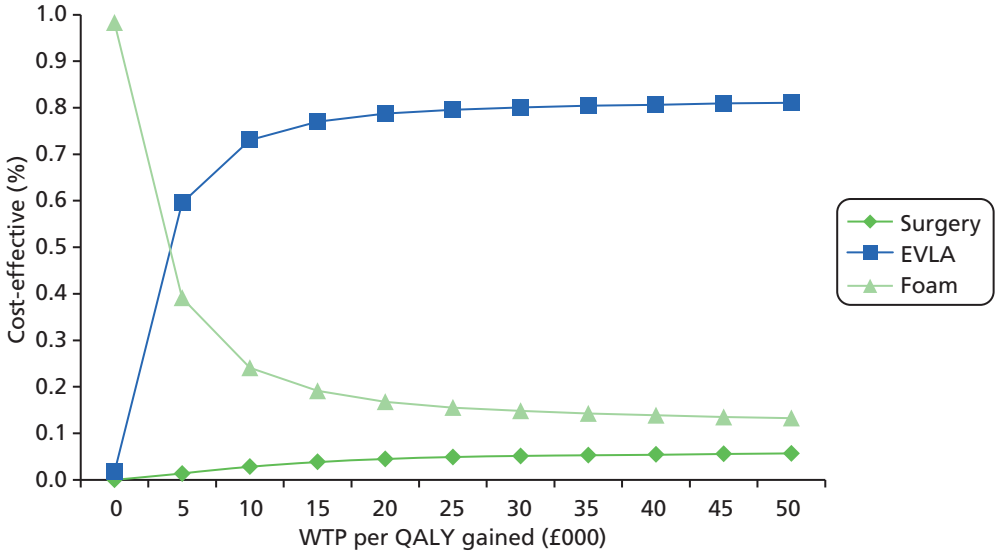

FIGURE 16 Cost-effectiveness acceptability curve based on 5-year time horizon.

TABLE 101 Base-case analysis over a 10-year time horizon

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Foam sclerotherapy	815	0	7.265	0	0	0.165
EVLA	1238	424	7.470	0.205	2065	0.76
Surgery	1475	237	7.332	−0.138	−1716	0.075

Note
Rc is ceiling ratio of WTP per QALY gained.

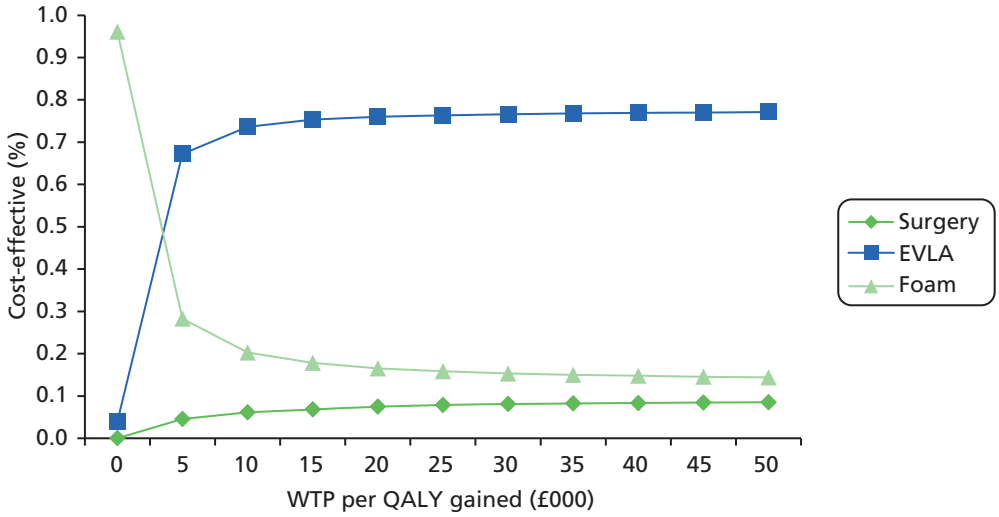

FIGURE 17 Cost-effectiveness acceptability curve based on 10-year time horizon.

TABLE 102 Deterministic sensitivity analysis results

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Scenario 1: including additional overhead costs for procedures carried out in theatre						
Foam sclerotherapy	684	–	4.000	–	–	0.174
EVLA	1122	438	4.119	0.118	3703	0.8
Surgery	1561	439	4.040	–0.078	Dominated	0.027
Scenario 2: cost and utility inputs based on full multiple imputation analysis						
Foam sclerotherapy	677	–	3.975	–	–	0.114
EVLA	1094	417	4.116	0.142	2943	0.769
Surgery	1237	144	4.057	–0.060	Dominated	0.116
Scenario 3: cost and utility inputs based on multiple imputation analysis, with participants receiving no treatment and follow-up dropped						
Foam sclerotherapy	665	–	3.996	–	–	0.174
EVLA	1097	432	4.115	0.119	3626	0.738
Surgery	1272	175	4.044	–0.071	Dominated	0.088
Scenario 4: applying cost and utility input parameter values based only on patients with unilateral disease and no simultaneous treatment to contralateral leg						
Foam sclerotherapy	646	–	3.990	–	–	0.172
EVLA	1081	436	4.138	0.148	2947	0.778
Surgery	1233	152	4.037	–0.101	Dominated	0.051
Scenario 5: applying cost and utility input parameter values based only on patients with unilateral disease and GSV involvement						
Foam sclerotherapy	646	–	3.929	–	–	0.115
EVLA	1085	439	4.107	0.179	2456	0.784
Surgery	1251	166	4.039	–0.069	Dominated	0.102
Scenario 6: 60% of patients with clinical recurrence proceed to further treatment						
Foam sclerotherapy	622	–	3.995	–	–	0.168
EVLA	1066	444	4.115	0.120	3702	0.786
Surgery	1262	196	4.035	–0.080	Dominated	0.046
Scenario 7: 90% of patients with clinical recurrence proceed to further treatment						
Foam sclerotherapy	706	–	4.006	–	–	0.168
EVLA	1124	418	4.123	0.117	3576	0.788
Surgery	1339	215	4.045	–0.077	Dominated	0.044
Scenario 8: all patients with clinical recurrence receive conventional surgery						
Foam sclerotherapy	734	–	3.999	–	–	0.169
EVLA	1143	409	4.118	0.119	3451	0.785
Surgery	1363	221	4.039	–0.079	Dominated	0.046

continued

TABLE 102 Deterministic sensitivity analysis results (*continued*)

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Scenario 9: all patients with clinical recurrence receive foam						
Foam sclerotherapy	603	–	3.997	–	–	0.17
EVLA	1053	450	4.116	0.119	3768	0.786
Surgery	1245	192	4.037	–0.079	Dominated	0.045
Scenario 10: application of NHS reference cost (£1216) to all treatments for clinical recurrence						
Foam sclerotherapy	755	–	4.000	–	–	0.169
EVLA	1157	402	4.119	0.118	3401	0.786
Surgery	1383	225	4.040	–0.078	Dominated	0.046
Scenario 11: 2-year delay between clinical recurrence and receiving further treatment						
Foam sclerotherapy	605	–	3.987	–	–	0.172
EVLA	1049	444	4.108	0.122	3656	0.782
Surgery	1242	192	4.027	–0.081	Dominated	0.047
Scenario 12: allowing any number of repeat treatments for subsequent clinical recurrences, with a 10-year time horizon						
Foam sclerotherapy	927	–	7.283	–	–	0.164
EVLA	1285	358	7.478	0.196	1831	0.765
Surgery	1547	262	7.345	–0.134	Dominated	0.071
Scenario 13: assuming no difference in post-treatment utility scores between alternatives						
Foam sclerotherapy	664	–	4.033	–	–	0.549
EVLA	1095	431	4.052	0.019	22,268	0.378
Surgery	1300	206	4.039	–0.013	Dominated	0.073
Scenario 14: assuming no difference in post-treatment utility scores between alternatives, with a 10-year time horizon						
Foam sclerotherapy	815	–	7.311	–	–	0.42
EVLA	1238	424	7.365	0.054	7881	0.454
Surgery	1475	237	7.328	–0.036	Dominated	0.127
Scenario 15: utility inputs based on participant responses to the SF-36 (scored using the SF-6D)						
Foam sclerotherapy	665	–	3.706	–	–	0.216
EVLA	1095	431	3.772	0.066	6503	0.782
Surgery	1301	205	3.706	–0.066	Dominated	0.003
Scenario 16: equal recurrence rates applied following EVLA and surgery						
Foam sclerotherapy	664	–	4.002	–	–	0.169
EVLA	1095	431	4.119	0.117	3691	0.78
Surgery	1255	160	4.053	–0.066	Dominated	0.052

Note
Rc is ceiling ratio of WTP per QALY gained.

cluster of patients in the surgery arm, receiving no treatment within CLASS, being assigned costs in line with the mean treatment cost (across all arms) in the imputation analysis. These patients were dropped out of the complete case analysis owing to withdrawal from follow-up. Using multiple imputation to put these patients back into the analysis reduces the mean cost of surgery and, consequently, increases its chances of being cost-effective. However, EVLA still retains the highest chance of being cost-effective. Further, when the patients receiving no treatment and no follow-up are dropped from the multiple imputation analysis, the relative order of the strategies is restored to that observed for the base-case analysis (see scenario 3 in *Table 102*). The base-case findings were also found to hold when restricting the analysis to patients with unilateral disease only and to patients with unilateral disease and GSV involvement only.

When applying the assumption of no difference in generic QALYs between the strategies up to 6 months, and no difference in the mean EQ-5D score at 6 months, foam sclerotherapy has the highest probability of being cost-effective at 5 years (see scenario 13 in *Table 102*), with EVLA second and surgery third. However, the base-case ordering is restored when the time horizon for this analysis is extended to 10 years (see scenario 14 in *Table 102*).

Secondary analysis for bilateral varicose veins

As well as assessing the sensitivity of the base-case cost-effectiveness findings to alternative parameter values and assumptions, a further model-based analysis was undertaken to ascertain the likely cost-effectiveness of using the alternative treatment modalities in patients with bilateral disease. Several assumptions were required for this analysis, as participants with bilateral disease in the CLASS trial were assigned only one study leg to be treated, in accordance with the CLASS protocol. Therefore, the CLASS data are not ideally suited to assessing the cost-effectiveness of using the individual treatment modalities (where clinically appropriate) to treat bilateral varicose veins.

To inform this analysis, it was assumed that QALY and utility gains following bilateral treatment would follow the same pattern as observed for the treatment of unilateral veins. This assumes that using the alternative treatment modalities in both legs would result in similar outcomes for both legs, and that the worst leg determines patients' QoL. It was further assumed that for surgery, treatment of both legs would be carried out in a single session, whereas for foam and EVLA the second leg would be treated in a separate session. Therefore, in this model the cost of surgery (for unilateral disease) was inflated by 1.23, the ratio of the mean surgery cost for unilateral disease over the mean surgery cost for patients in the CLASS trial having surgery for their contralateral leg at the same time. For foam and EVLA, we added the full cost of an additional treatment session, based on the mean cost estimates for unilateral treatment derived from the trial data. These assumptions are conservative in favour of surgery, as EVLA may also be carried out for the second leg within a single treatment session.

Finally, to reflect the fact that costs associated with clinical recurrence are likely be higher in patients with bilateral disease, we applied the NHS reference cost (£1611) for the treatment of recurrent bilateral varicose veins.[86]

The results of this analysis are presented in *Table 103*. They show that under this scenario EVLA becomes the most costly option. However, as a result of application of the estimated QALY and utility gains for EVLA versus surgery in the model, and application of a slightly lower estimated recurrence risk for EVLA, EVLA retains an estimated QALY gain of 0.1 over surgery at 5 years. The consequence of this is that EVLA has an ICER below £20,000 in comparison with surgery, and the highest chance of being cost-effective at this threshold.

The impact on the results of applying the same EQ-5D utility weight for surgery and EVLA at 6 months and beyond (see scenario 2 in *Table 103*), and of applying the same clinical recurrence risk (see scenario 3 in *Table 103*), was also assessed. The findings are robust to these changes individually, but when applied simultaneously, the ICER for EVLA rises above £20,000 per QALY gained, and surgery has the higher chance of being cost-effective (see scenario 4 in *Table 103*).

TABLE 103 Results of modelled scenarios for single modality treatment of bilateral disease

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Scenario 1: base-case bilateral treatment scenario						
Foam sclerotherapy	1137	–	3.990	–	–	0.206
Surgery	1631	493	4.037	0.047	10,440	0.09
EVLA	1953	323	4.138	0.101	3207	0.704
Scenario 2: applying the same EQ-5D utility weight for EVLA and surgery at 6 months						
Foam sclerotherapy	1137	–	3.990	–	–	0.204
Surgery	1631	493	4.105	0.115	4290	0.249
EVLA	1953	323	4.138	0.033	9799	0.574
Scenario 3: applying the same recurrence risk for EVLA and surgery						
Foam sclerotherapy	1137	–	3.990	–	–	0.204
Surgery	1548	411	4.050	0.060	6891	0.111
EVLA	1953	406	4.138	0.088	4591	0.685
Scenario 4: applying scenarios 2 and 3 simultaneously						
Foam sclerotherapy	1137	–	3.990	–	–	0.21
Surgery	1548	411	4.121	0.131	3128	0.505
EVLA	1953	406	4.138	0.017	24,341	0.284

Sensitivity to alternative structural assumptions

Table 104 and *Figure 18* summarise the results obtained when using alternative structural assumptions to construct the model. With this model, it was assumed that the alternative treatments have no differential impact on the generic HRQoL of patients, other than that driven by their effects on the clinical severity of patients' venous disease (as assessed by the VCSS).

In line with the clinical analysis of the VCSS score, this model predicts higher QALYs with EVLA than with foam, and slightly higher QALYs with surgery than with EVLA. However, the incremental cost per QALY gained with surgery versus EVLA remains slightly above £30,000 at 5 years, and, consequently, the probability of surgery being cost-effective remains lower than that for EVLA at the ceiling ratio of £20,000 per QALY. Furthermore, increasing the time horizon for this analysis to 10 years (*Table 105*, *Figure 19*) increases the chance of EVLA being the preferred option owing to its slightly lower estimated clinical recurrence rate.

TABLE 104 Secondary analysis over a 5-year time horizon

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Foam sclerotherapy	667	–	4.022	–	–	0.302
EVLA	1096	429	4.063	0.042	10,329	0.397
Conventional surgery	1301	205	4.070	0.006	31,977	0.301

Note
Rc is ceiling ratio of WTP per QALY gained

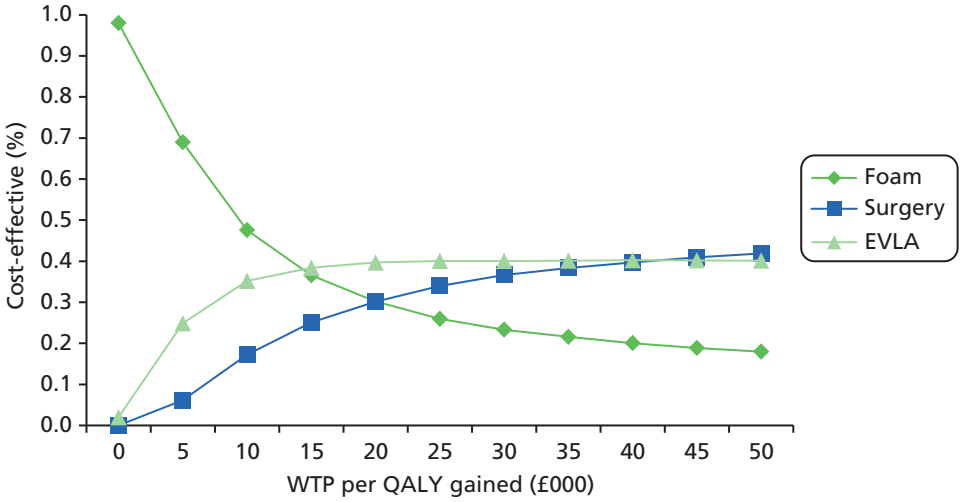

FIGURE 18 Cost-effectiveness acceptability curve based on the alternative model structure with a 5-year time horizon.

TABLE 105 Secondary analysis over a 10-year time horizon

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	Incremental cost per QALY (£)	Probability cost-effective at Rc £20,000
Foam sclerotherapy	817	–	7.314	–	–	0.251
EVLA	1240	422	7.409	0.094	4474	0.440
Conventional surgery	1476	237	7.406	–0.003	Dominated	0.309

Note
Rc is ceiling ratio of WTP per QALY gained.

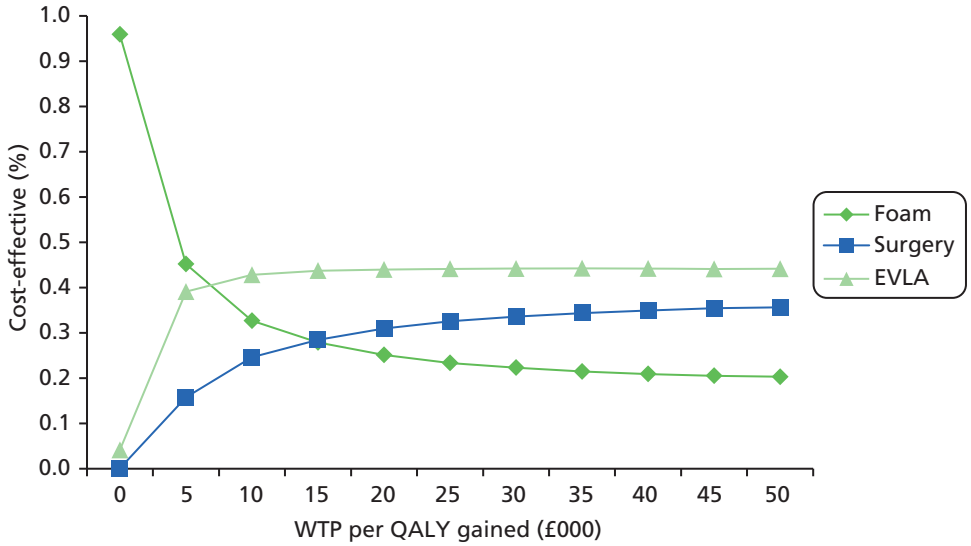

FIGURE 19 Cost-effectiveness acceptability curve based on the alternative model structure with a 10-year time horizon.

Given the slightly counterintuitive impact of applying the observed mean EQ-5D utility scores for patients in clinical severity states 3 and 4 following primary treatment (the mean values for these states were lower post treatment than they were pre treatment, resulting in modelled recurrence leading to a utility increase for some patients), we also examined the impact of applying the mean EQ-5D utility values obtained across the baseline and 6-months time points for these states in the model. This had very little impact on the results (*Figure 20*).

Discussion

Summary of key results

The modelling in this chapter suggests that, over a 5- and 10-year time horizon, EVLA is likely to be the preferred option on grounds of cost-effectiveness, costing only £3640 per QALY gained in comparison with foam sclerotherapy, and costing less and producing slightly more QALYs than surgery. Based on probabilistic analysis, EVLA had a ≈ 79% chance of being cost-effective at a ceiling WTP ratio of £20,000 per QALY.

These findings, based on extrapolation of the incremental costs and outcomes obtained from the analysis of complete trial data, were generally found to be robust to uncertainty surrounding various model parameter inputs and assumptions, including multiple imputation of missing data and the basing of model inputs on patients with unilateral disease. Although the CLASS data are not ideally suited to assessing the cost-effectiveness of the alternative treatment modalities for patients with bilateral disease (where clinically appropriate), a further sensitivity analysis was carried out to address this question, applying a number of different assumptions (see *Table 103*). Under most of the scenarios, EVLA retained the highest probability of being cost-effective. However, when it was assumed that EVLA and surgery have exactly the same utility outcome at 6 months, and also the same clinical recurrence rate, surgery had the higher chance of being cost-effective. This last result was still based on the conservative assumption (favouring surgery) that when using EVLA to treat bilateral disease, treatment of the second leg would generally be carried out in a separate treatment session. Therefore, it is likely that EVLA should also be preferred on grounds of cost-effectiveness for the treatment of bilateral disease in situations where all three treatment modalities are clinically viable options for the treatment of both legs.

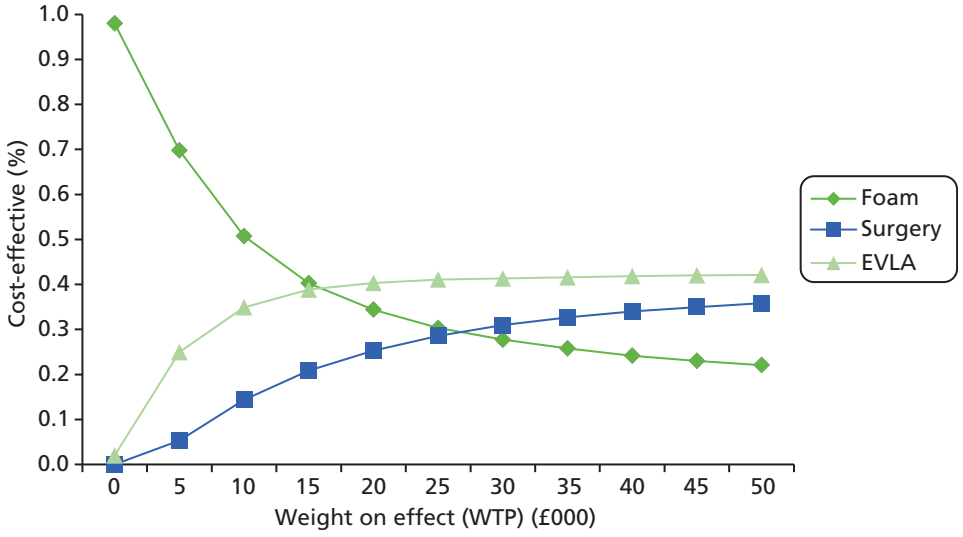

FIGURE 20 Cost-effectiveness acceptability curve based on the alternative model structure with a 5-year time horizon (assuming equal utility for states 3 and 4 both pre and post treatment).

The model-based probability of EVLA being the preferred option at the ceiling WTP ratio of £20,000 per QALY was found to be somewhat sensitive to the application of alternative model structuring assumptions. The base-case model extrapolated estimates of the direct effects of the alternative treatments on generic HRQoL (as measured by the EQ-5D). This translated into a small gain in QALYs for EVLA over surgery which, coupled with the lower cost of EVLA, resulted in it having a high probability of being cost-effective compared with surgery. However, the estimated QALY and utility gains associated with EVLA were not significant at 6 months. Therefore, we assessed the impact of (1) setting equal utility gains following the alternative treatment options; and (2) mapping changes in utility to transitions across health states defined by the VCSS. Both these approaches resulted in greater uncertainty surrounding selection of optimal treatment modality on grounds of cost-effectiveness. However, EVLA did retain the higher probability of being cost-effective at the WTP threshold of £20,000 per QALY.

Explanation of findings

The finding that EVLA has the highest chance of being the most cost-effective option is driven by a number of factors: (1) its greater estimated QALY and utility gains at 6 months versus foam sclerotherapy and, to a lesser extent, surgery; (2) its lower cost at 6 months compared with surgery; and (3) its slightly lower estimated clinical recurrence rate compared with foam sclerotherapy and surgery. Although none of the estimated differences between EVLA and surgery (with respect to post-treatment EQ-5D values and the probability of recurrence) were significant at the traditional 5% level, it was the mean estimates or estimated mean differences (between the alternative treatment modalities) that were used as model inputs (with the uncertainty surrounding each input appropriately characterised as a probabilistic distribution). The uncertainty surrounding each model parameter was then simultaneously propagated through the model (using 10,000 probabilistic iterations) to characterise the uncertainty surrounding the model outputs, that is, the estimated mean costs and effects of the alternative treatment modalities. This uncertainty surrounding the model outputs was then expressed as a probability of each strategy being cost-effective when using a ceiling ratio of £20,000 to value the model outcome (QALYs).

Strengths and limitations

The model was populated, where possible, using estimates of the mean difference in costs and effects derived from the analysis of individual patient data on resource use and outcomes collected prospectively alongside the CLASS study. Therefore, the results should be internally valid and generalisable across settings in the UK.

In the absence of data on long-term clinical recurrence for the CLASS cohort, the risk of clinical recurrence was modelled using data derived from a network meta-analysis of existing trials which reported clinical recurrence as an outcome.[28] Although this provides the best current source of evidence on recurrence, the quality of trials included in this network meta-analysis varied, and EVLA and endothermal radiofrequency ablation were pooled for the analysis. In addition, some RCTs included subjects undergoing only high tie without stripping, which would result in a higher clinical recurrence rate. In CLASS, all patients had preoperative scans to determine the involvement of single or multiple truncal veins, and all affected truncal veins were stripped. Furthermore, follow-up generally extended to only 12 or 24 months in the included trials (only one small trial[94] reported outcomes at 36 months) and definitions of clinical recurrence were not always well defined and varied from study to study. Therefore, uncertainty remains regarding the applicability of these recurrence rates to patients in the CLASS trial (and more generally), and also the risks of recurrence beyond 24 months and the utility impact of clinical recurrence according to varying definitions. This underlines the importance of collecting further data on clinical recurrence and its impact on generic HRQoL via the extended follow-up of CLASS participants. Plans are in place to do this at 5 years, which will provide a means of validating and updating the modelling undertaken in this chapter.

Comparison with other cost-effectiveness studies

In general, the modelling approach used in this chapter is consistent with that used in previous economic modelling studies of treatments for varicose veins. Michaels *et al.*[65] previously developed a Markov model to assess the cost-effectiveness of conventional liquid sclerotherapy in comparison with surgery for patients

with moderate and severe uncomplicated varicose veins. Four severity states were defined using an anatomical classification combined with evidence for the presence/absence of reflux, which was used to estimate the risk of subsequent clinical recurrence. The clinical severity states were defined as pre- and post-treatment states, in a similar manner to the way in which the clinical states were defined in the secondary analysis model described in this chapter. However, the states in our model were based on the VCSS rather than the anatomical distribution of varicose veins. In addition, Michaels *et al.*[65] assigned the same utility weights (obtained from post-treated patients) to their severity states both pre and post treatment (owing to a lack of correlation between baseline utility values and the anatomical health states). This may have resulted in a lack of sensitivity for capturing changes in utility associated with remaining in the same severity state following treatment.

A further difference between the CLASS and Michaels models relates to the fact that Michaels *et al.*[65] explicitly included some complications of surgery and sclerotherapy in their model, whereas the impact of any complications was implicitly captured in the models described in this chapter by applying the mean costs and QALYs observed for patients enrolled in the CLASS trial at 6-months follow-up. Further, observed utility at 6 months was extrapolated beyond this time point, and was assumed to capture the utility impact of any differences in complication rates between the treatment options at 6 months and beyond.

Based on their model, Michaels *et al.*[65] reported an ICER for surgery versus conventional liquid sclerotherapy of £1728 per QALY based on a 10-year time horizon. However, the relevance of this prior analysis is now questionable as foam sclerotherapy has superseded the use of conventional liquid sclerotherapy. Furthermore, for purposes of decision-making, it is not appropriate to consider the relative cost-effectiveness of sclerotherapy and surgery in isolation of the other appropriate comparator, EVLA.

Gohel *et al.*[54] similarly developed a Markov model to assess the cost-effectiveness of conservative management, foam sclerotherapy, EVLA, RFA and surgery. This was a simpler model than that developed by Michaels *et al.*,[65] simulating the continued success or recurrence of reflux in patients following either a completely successful or a partially successful (residual varicosities or incomplete occlusion) primary treatment. The effects of the alternative treatments on initial outcome at 3 months and subsequent recurrence of reflux were based on reviews of existing RCTs, and the costs of treatments were adapted from NHS reference costs.[86] Finally, health state utilities associated with primary varicose veins and successfully treated varicose veins were taken from a previous trial of surgery. It was assumed that patients not experiencing a successful primary treatment would remain at the pre-treatment utility level, but that those patients with residual varicosities would be offered additional foam sclerotherapy (assumed successful) and those with incomplete occlusion at 3 months would receive another treatment with the same probability of success as the primary treatment.

Based on this model, Gohel *et al.*[54] estimated that EVLA carried out under local anaesthetic would have the highest chance of being cost-effective at a ceiling ratio of £20,000 per QALY, with day-case surgery having the next highest probability, followed by RFA and foam sclerotherapy. Although the finding that EVLA has the highest probability of being cost-effective is consistent with our analysis, the probabilistic ordering of strategies from the model by Gohel *et al.*[54] was somewhat different to ours. Although it is difficult to unpick all the reasons for this, it may be partly explained by the fact that Gohel *et al.*[54] used estimates for the recurrence of reflux as the QoL driver (rather than clinical recurrence) and also applied less precise costs to their alternative treatment modalities (basing these on NHS reference costs). Furthermore, differences in model structure may also explain the differences in findings.

The structure and assumptions applied in our primary analysis are more in line with those used in the model developed to inform the recent NICE Clinical Guideline 168.[28] However, some differences do exist in terms of the cost and utility estimates applied in the models. Based on the direct collection of individual patient-level resource use data through CLASS CRFs and questionnaires, combined with a survey of participating centres to collect information on additional resource use, we estimated a somewhat narrower difference in cost between EVLA and surgery compared with that inferred from the estimates used in the

NICE guideline model. This was due to differences in our estimated mean treatment durations (based on prospectively collected patient-level data) as well as differences in the reported staffing profile for the different procedures. Our estimates are more likely to be generalisable to UK practice because they were derived using time and staffing data collected prospectively alongside the CLASS trial rather than clinical opinion. Furthermore, rather than assuming equal utilities following different treatment modalities at 6 months (as was done in the NICE guideline model), we applied the estimated mean incremental differences between foam and surgery and between EVLA and surgery. For the first 6-month cycle, the model was also specified to return the mean QALYs observed for patients in alternative treatment allocation arms of the CLASS trial.

Despite the differences between our analysis and that used to inform development of NICE Clinical Guideline 168, the conclusions of our analysis are generally similar. EVLA retained the highest probability of being cost-effective under most scenarios tested. However, the NICE guideline also concluded that foam sclerotherapy would be the most cost-effective option in situations where EVLA is not considered a viable option, based on an ICER for surgery versus foam > £20,000 per QALY gained. Although our modelling was based on data that do not allow us to directly address this question (suitability for all three treatment modalities was an inclusion criteria in the CLASS trial), it does indicate that, for the CLASS cohort, the incremental cost per QALY gained for surgery versus foam is generally below £20,000.

Conclusion of model-based cost-effectiveness analysis

Overall, our modelling suggests that for patients in whom all three treatment modalities are a clinically viable option, EVLA has the highest probability of being cost-effective at accepted thresholds of WTP per QALY. This finding is consistent with the results of recent modelling undertaken to inform the NICE clinical guideline on the management of varicose veins. However, we cannot rule out the possibility that surgery may be the preferred option in patients in whom EVLA is not viable. We cannot directly address this question, as our modelling was based on cost and utility inputs derived from patients eligible for all three treatment options.

Chapter 11 Final discussion

The CLASS trial has shown that at 6-months follow-up all three treatment modalities – foam, EVLA and surgery – improved disease-specific and generic QoL and achieved similar improvements in the VCSS. EVLA and surgery were broadly equivalent in terms of the improvements in disease-specific QoL, VCSS and anatomical success (ablation of GSV or SSV trunks). However, EVLA showed greater early improvements in four of the eight SF-36 domains than surgery, although these were not present at 6 months.

In this first RCT involving foam sclerotherapy to evaluate and report disease-specific QoL as a primary outcome measure, the health gain achieved with foam sclerotherapy was significantly lower than that for surgery at 6-months follow-up. At 6 weeks the health gain in the AVVQ was also significantly lower for foam sclerotherapy than for surgery. At 6 months, the health gain in the SF-36 mental component was also significantly lower for foam sclerotherapy than for EVLA. The EQ-5D health gain with foam sclerotherapy at 6 weeks was also significantly lower than with EVLA, but there were no differences at 6 months.

As well as having lower QoL health gains, patients who had foam sclerotherapy had more residual varicose veins than those undergoing EVLA or surgery at 6-months follow-up. Foam sclerotherapy was also associated with a significantly greater rate of procedural complications than EVLA, and of complications at 6 weeks than surgery and EVLA. At 6 months, the overall complication rate remained higher for foam sclerotherapy than for surgery. However, the recovery and return to normal activities was quicker for foam and EVLA than for surgery. Furthermore, at 6 weeks patients' recollection of the pain experienced at the time of the procedure and in the recovery was less following foam sclerotherapy than either EVLA or surgery.

The anatomical success rate was significantly lower for foam sclerotherapy than for surgery or EVLA. This is likely to result in a greater risk of developing recurrent varicose veins and need for further treatment in patients who underwent foam sclerotherapy. In contrast, the trial-based cost-effectiveness analysis showed that at 6 months foam sclerotherapy had the lowest costs, followed by EVLA and then surgery. Based on consideration of costs and QALYs at 6 months, foam sclerotherapy had the highest probability of being considered cost-effective at the accepted Rc of £20,000 per QALY. However, foam sclerotherapy was not associated with the greatest clinical benefit.

Some differences were evident between the cost estimates incorporated in our analysis and those used in the recent NICE guideline.[28] We estimated a somewhat larger cost difference between foam sclerotherapy and EVLA, whereas a somewhat smaller cost difference was estimated between EVLA and surgery. The main reason for this was that in some centres within the CLASS trial EVLA was performed in a theatre setting, which required a larger number of staff to be present, whereas in others it was performed in a clinic setting, which used the same staff profile as foam. A sensitivity analysis was conducted to test the impact of EVLA incorporating a similar staff profile to foam sclerotherapy. Under this scenario, the ICER of EVLA versus foam sclerotherapy fell below the accepted threshold of £20,000 per QALY gained. Further, the cost saving from EVLA versus surgery significantly increased. Thus, when EVLA was performed in a clinic setting with a similar staff profile to that used for foam, it produced the greatest NMB at 6 months compared with both foam sclerotherapy and surgery.

However, these early results cannot be used to determine definitive recommendations for the treatment of varicose veins because late recurrence rates and the need for further treatment also need to be considered. This is a very important determinant of cost-effectiveness in the longer term. This underlines the importance of the 5-year follow-up of patients in the CLASS study.

Markov modelling based on the trial data and the limited data currently available on longer-term recurrence rates suggests that, at 5 years, EVLA has the highest probability of being cost-effective (≈ 79%), followed by foam sclerotherapy (≈ 17%) and surgery (≈ 5%), for patients considered clinically suitable for all three treatment options. It should be noted, however, that the outcome of this model is quite sensitive to the projected recurrence rates. Data from clinical recurrence rates at 5 years are not available from controlled trials at present, with the exception of the recent study by Rasmussen[51] comparing EVLA with surgery. The recurrence rates used for the CLASS modelling were based on figures used in the recent NICE economic analysis.[28] Using these assumptions, our analysis suggests that EVLA is likely to be the treatment of choice for suitable patients, based on considerations of both clinical effectiveness and cost-effectiveness. Although the CLASS findings are not directly applicable to patients considered clinically unsuitable for EVLA (suitability for all three treatment options was an inclusion criterion in the CLASS trial), our modelling does suggest that the incremental cost per QALY gained with surgery versus foam sclerotherapy will fall below £20,000 by 5 years in the CLASS cohort. In a two-way comparison between foam sclerotherapy and surgery, we found surgery to have the higher probability of being cost-effective at 5 years, although a great deal of uncertainty surrounds this finding owing to the significantly higher cost of surgery and uncertainty relating to its generic QoL and longer-term benefits over foam.

If the above model-based findings are confirmed by long-term follow-up of the CLASS cohort, and considered generalisable to patients not suitable for EVLA, then conventional surgery may be preferred over foam sclerotherapy on grounds of cost-effectiveness in these patients. Furthermore, other clinical benefits, such as the significantly greater improvement in disease-specific QoL, reductions in some complications at 6 months and the higher anatomical success rate associated with surgery, may also be considered when determining the choice of treatment for patients not suitable for EVLA. The recent NICE clinical guideline,[28] which recommends foam sclerotherapy as the preferred treatment in patients who are not suitable for EVLA, therefore presents a dilemma for clinicians, patients and commissioners in terms of balancing clinical effectiveness, patient choice and cost when choosing which treatments to offer if the patient is not suitable for EVLA.

Strengths and limitations

Proportion of ineligible patients and overall recruitment rates

In this study, 43% of screened patients were found to be ineligible for inclusion in the trial. The main reason for this was the presence of recurrent varicose veins (28%) and the lack of truncal GSV or SSV reflux (22%). The proportion of ineligible patients is higher than in previous studies, where review of case notes or other methods of screening in advance of the patient's appointment may have been used. The lack of advance screening in CLASS is evident from the number of patients who were excluded because they either had recurrent veins or did not have symptomatic varicose veins.

Of the eligible patients, only 24% were recruited to CLASS. This is lower than most of the previously published RCTs involving varicose veins,[38,40,50] although the 2007 Rasmussen study[36] only achieved an 11% recruitment rate and the study by Darwood *et al.*[15] failed to reach its recruitment target. A previous HTA-funded study involving vascular surgeons recruiting patients with severe limb ischaemia also experienced similar recruitment rates to the CLASS study (29%), and this was attributed to a lack of clinical equipoise.[98]

Among the patients who were eligible but declined to take part, 78% either had a preference for one of the treatment options or did not wish to undergo one of the treatment options within the study. More patients declined to take part in the study because they wanted surgery (33%) than declined because they did not want surgery (< 1%). For EVLA, a similar proportion of patients expressed a preference (30%) and 1% declined because they did not want this treatment. In contrast, the proportion of patients who preferred foam sclerotherapy was much lower (preference for foam 13%). Clearly, many factors may have affected a patient's decision to take part in the study and preference for one treatment over another.

Although surgeon preference was cited infrequently as a reason (1%), the treating vascular surgeon is likely to have had a significant influence on the patient's decision-making.

In order to explore this further, a study was performed at one of our sites. This found that the surgeons presented balanced descriptions of the treatments but that they made the assumption that the patients might have a preference, and patients, in turn, felt that they were expected to have a preference.

Revised target sample size

The original trial sample size of 1015 (surgery vs. foam, 90% power, 5% significance, EVLA, EVLA versus foam or surgery 80% power, 5% significance) was revised to 779 based on data which showed that the correlation between AVVQ at baseline and at 6 months was better than originally assumed. This analysis was prompted by the lower than expected recruitment rate. The reduction in sample size did not lead to any reduction in the predefined clinically important difference in QoL, but may have disadvantaged the EVLA arm in which the power was lower. This revision was approved by both the TSC and DMC.

Number of statistical comparisons

There were a large number of comparisons involving primary and secondary outcomes, and therefore it may be inferred that some differences may have occurred by chance. Thus, for the secondary outcome measures, we consider differences to be significant only for p-values < 0.005.

Generalisability

Despite the fact that many eligible patients chose not to take part, those who did participate appear broadly similar to those in other RCTs (see *Chapter 7*), with the exception of a lower than expected proportion of females (56% of participants were female, but 75% of those invited to participate were female). Although most (or all) of the previous RCTs involving varicose veins have had higher proportions of female participants, our experience is consistent with a number of other studies which have shown that females are less likely than males to participate and are more difficult to recruit to RCTs.[99–104] It has been suggested that this may reflect less favourable attitudes towards medical research among women. It is of note that the mean baseline AVVQ score for women was slightly higher than for men (18.2 vs. 17.4), although this difference was not statistically significant and was unlikely to have had a bearing on their recruitment to the study.

The CEAP classification grade, VCSS (pre/post treatment) and QoL (pre/post treatment) were similar to those in other RCTs.[15,29–34,37,38,49–51] The QoL values were also similar to those published in NHS England PROMs. Given this, and the fact that less than 20% of patients were excluded because the vein diameter was too small, large or tortuous, the results of this study appear generalisable to the majority of patients seeking treatment for primary varicose veins.

Truncal ablation rates

The reasons for the lower ablation rates observed in the CLASS study compared with previous reports have been fully discussed in *Chapter 7*. Although the complete success rates for the GSV are at the lower end of those published in other RCTs, many of these defined 'technical success' as the combination of complete ablation and partial success with no reflux. The overall 'technical success' rate for CLASS is comparable (91% for EVLA and 82% for surgery). The results for foam (67% complete and partial with no reflux) remain lower than in some studies, but are comparable with those in the RCT by Latimer *et al.*[32] and those achieved by surgeons in the study by Wright *et al.*[14] It is important to note that, despite the apparently lower ablation rates, the improvements in QoL and VCSS were comparable with those published in previous RCTs[15,29–34,37,38,49–51] and in the PROMs for NHS England. In addition, this is the largest multicentre RCT to date involving EVLA, foam and surgery, and its results reflect those of the generality of vascular surgeons and their trainees, rather than those of enthusiasts in single centres.

Unlike those in previous RCTs, the duplex scans by which truncal ablation was assessed were performed by independent, accredited vascular technologists, with the exception of those performed at one centre. This was done in order to minimise the bias which can occur when surgeons who have treated patients do the follow-up scans. An attempt was made to quality assure the scans, but as none of the sites were able to video-record a whole examination, this proved impossible. An audit of still images taken at set anatomical locations was of no value owing to the lack of anatomical landmarks on the images, which meant that the duplex scanning site could not be verified. There was also no means of standardising the angle of the probe, or probe or calf compression. These difficulties reflect the general limitations of duplex scanning and are not specific to our study. The technique for performing the scan was standardised prior to commencing the trial following discussion between the vascular technologists at the 10 centres, and results were recorded on a set proforma. These dedicated vascular technologists are likely to be more skilled and reliable than the varied clinicians who scanned in other studies.

Concomitant phlebectomies

The issue of whether or not varicosities should be treated at the same time as the main truncal veins remains controversial. This is highlighted as an area of future research in the recent NICE clinical guideline.[28] One previous single-centre RCT has shown significant improvements in disease-specific QoL and VCSS at 6 weeks and 3 months following concomitant, as opposed to delayed, phlebecotomies.[73]

In CLASS, patients in the EVLA group only received treatment to the main truncal vein, without concomitant phlebectomies (with the exception of patients at one site), unlike those in the surgery group. Nevertheless, we observed significant improvements in the AVVQ and VCSS in patients undergoing either surgery or EVLA compared with foam sclerotherapy at 6 weeks. Importantly, there was no difference in these outcomes in patients undergoing EVLA or surgery at the 6-weeks follow-up. These findings suggest that the strategy of performing concurrent phlebectomies in patients undergoing EVLA is unnecessary, with respect to improving QoL or VCSS in the short term. Furthermore, approximately one-third of patients who underwent EVLA in CLASS elected to have treatment for residual varicosities at or after 6-weeks follow-up, so it could be inferred that the use of concomitant phlebectomies would have been unnecessary treatment for the remaining two trials of participants. It is unclear if this will affect future recurrence rates.

The CLASS trial also raises concerns regarding whether or not foam sclerotherapy is the most appropriate means to treat any residual varicose veins. EVLA showed benefits over foam sclerotherapy in terms of disease-specific and generic QoL as well as reduced complications at 6 weeks. These benefits did not persist to 6 months, by which stage one-third of the patients in the EVLA group had undergone foam sclerotherapy.

Clinical, etiological, anatomical, pathological grade

The majority of patients in the CLASS study had CEAP grade 2 varicose veins, which is consistent with other studies and with the known distribution of venous disease in the population. NICE referral guidelines for varicose veins published in 2001 recommended referral of symptomatic primary varicose veins, which are associated with impaired QoL.[105] It is apparent that rationing is being imposed in most areas, which means that only patients with more severe CEAP grades are offered referral for treatment. Thus, the results from CLASS may not be as generalisable to current NHS practice as they should be if referral guidelines were adhered to. The study was designed before this rationing became widespread. Within CLASS, there was evidence of a clear inequity in the provision of treatment for varicose veins in centres across the country, which has arisen primarily as a result of cost pressures and, indeed, this influenced differences in recruitment rates between centres. It is not clear what the long-term health and QoL effects of not treating many people with varicose veins will be. If it does lead to an increased incidence of venous ulceration, this will have substantial cost consequences for the NHS, in addition to increased morbidity and decreased QoL for affected patients.

Sensitivity of the European Quality of Life-5 Dimensions to detect differences between treatment modalities

As would be expected in patients undergoing treatment for varicose veins, the AVVQ, designed specifically to assess QoL in these patients, was more sensitive to change than either of the generic QoL instruments (SF-36 and EQ-5D). This sensitivity was demonstrated in terms of the magnitude of change from baseline at both 6 weeks and 6 months post treatment and was crucial in confirming improvements both across and between the treatment groups. The AVVQ showed differences between groups at 6 weeks which favoured surgery and EVLA over foam sclerotherapy, and differences at 6 months which favoured surgery over foam sclerotherapy. By contrast, the EQ-5D showed only a benefit for EVLA over foam sclerotherapy at 6 weeks but no differences at 6 months. However, the EQ-5D was principally used in the evaluation of cost-effectiveness as it is the instrument routinely used for this type of QoL analysis.[28]

Lack of inclusion of radiofrequency ablation as a treatment option

We chose to include EVLA and foam sclerotherapy in the CLASS trial because these were the two most widely used of the newer, local anaesthetic treatment options within the NHS at that time. We considered RFA as an alternative to EVLA, but it was more costly and less suited for local anaesthesia owing to the longer contact time required between the probe and the vein endothelium. In addition, EVLA seemed to be in greater demand from patients and to have found favour with more vascular specialists at the time when the trial was being designed. However, subsequent developments have made RFA faster, such that it is now routinely performed under a local anaesthetic. Nevertheless, it remains more expensive than EVLA.

Endovenous laser ablation and RFA are now considered to be comparable techniques in terms of outcome. Furthermore, in the recent NICE Clinical Guideline 168[28] RFA was considered equivalent to EVLA; the two treatments were grouped together throughout the recommendations as ‘endothermal ablation’.

Behavioural recovery

The 14-item BRAVVO questionnaire was made up of items and behaviours which patients identified as being important to their recovery, many of which have not been considered in previous studies. Development of the BRAVVO instrument represents an important first step in identifying the behaviours that patients perceive to be important and will allow for a more detailed explanation to patients of the anticipated recovery following treatment, as well as a more sensitive comparison of the effect of different treatments on recovery.

Comparison of LAser, Surgery and foam Sclerotherapy 5-year follow-up

Treatment of recurrent varicose veins accounts for 20% of venous procedures performed in the NHS, and was responsible for ineligibility in 28% of patients considered for this trial; thus, the durability of primary treatment is important both for patients and for economic reasons. Few RCTs involving foam sclerotherapy or EVLA have assessed clinical recurrence rates, and they provide only limited short- to medium-term (i.e. 2-year) clinical results. The 5-year recurrence rate for EVLA has recently been reported in one small RCT[51] but has not been reported for any RCT of foam sclerotherapy.[14,29–33,51] Patients with recurrent varicose veins have significantly worse QoL than patients with primary varicose veins[106] and show less improvement in QoL after treatment,[7,107] so using a primary treatment which minimises the risk of recurrence is an important consideration.

Implications for practice

The CLASS trial has shown that EVLA (performed under a local anaesthetic, in a predominantly clinic-based setting) has the highest probability of being cost-effective at accepted thresholds of WTP per QALY. This finding is consistent with the results of recent modelling undertaken to inform the NICE clinical guideline[28]

on the management of varicose veins. The CLASS trial cannot directly inform the choice between surgery and foam in patients in whom EVLA is not a treatment option, as eligibility for all three treatment options was an inclusion criterion of the CLASS trial. However, less than 20% of patients were ineligible for the CLASS trial because the vein was too tortuous (9%), or either too small or too large in diameter (9%). Thus, the majority of patients with primary veins referred for treatment in the NHS appear to be suitable for thermal ablation. Furthermore, in CLASS only one eligible potential participant declined to be randomised because he/she did not wish to undergo EVLA.

For patients in whom thermal ablation may be unsuitable or declined, the results from the CLASS trial suggest that surgery rather than foam sclerotherapy should be considered. In a two-way comparison between foam and surgery, surgery was found to have the greatest probability of being cost-effective at 5 years, although a great deal of uncertainty surrounds this finding owing to the significantly higher cost of surgery and lack of long-term recurrence rate data for both interventions. However, surgery was associated with greater gains in the AVVQ at 6 months, a higher truncal ablation rate and reduced residual varicose veins compared with foam sclerotherapy. There were no differences in terms of the VCSS or complication rates, but return to normal activities was quicker following foam sclerotherapy than following surgery.

The CLASS trial also raises concerns regarding whether or not foam sclerotherapy is the most appropriate means to treat non-truncal varicosities in patients undergoing EVLA.

Recommendations for research

The CLASS trial has highlighted the need for long-term outcome data from RCTs on QoL, recurrence rates and costs for foam sclerotherapy and other endovenous techniques, compared against each other and against surgery. With one recent exception,[51] follow-up from RCTs involving foam sclerotherapy or EVLA is currently limited to 2 years. In the current absence of data on long-term clinical recurrence, the risk of clinical recurrence in CLASS was modelled using the network meta-analysis performed by NICE[28] which included recurrence rates up to 2 years. Although this provides the best current source of evidence on recurrence, uncertainty remains regarding the applicability of these recurrence rates to patients in the CLASS trial and the risks of recurrence beyond 24 months. This underlines the importance of collecting further data on clinical recurrence and its impact on generic QoL via the extended follow-up of CLASS participants.

We have previously discussed the controversial issue of whether or not varicosities should be treated at the same time as the main truncal veins. The CLASS trial provides further impetus for future research in this area as highlighted in the recent NICE clinical guideline.[28]

Conclusion

The CLASS trial is the largest multicentre trial to have compared surgery with the two most commonly performed newer treatment options, namely foam sclerotherapy and thermal ablation by EVLA. It has comprehensively assessed both the clinical effectiveness and cost-effectiveness of these treatment options within the NHS. The 6-month outcomes and 5-year economic model clearly suggest that EVLA should be considered as the first-line treatment in patients with varicose veins. In patients not suitable for EVLA, surgery rather than foam sclerotherapy should be considered on grounds of clinical effectiveness and cost-effectiveness.

We await the 5-year results of CLASS, which are essential to determine recurrence rates and the true cost-effectiveness of EVLA, foam sclerotherapy and surgery.

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Seonaidh C Cotton (trials manager, triallist) was responsible for the day-to-day management of the trial, contributed to the interpretation of data and made significant contributions to drafting the monograph.

Andrew Elders (statistician) conducted the statistical analyses, contributed to drafting the statistical methods section in *Chapter 3*, drafted the clinical effectiveness results in *Chapters 4–6* and reviewed the final manuscript.

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Jill Francis (health psychologist) led on the conception and design of the study of behavioural recovery and development of the BRAVVO questionnaire; contributed to analysis and interpretation of behavioural data and illness representations data; made significant contributions to drafting the BRAVVO chapter of the monograph and contributed to drafting the other chapters; and gave approval of the version to be published.

Samantha Wileman (quality assurance manager) contributed to oversight and conduct of the study, and preparation of the monograph.

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Appendix 1 Trial paperwork

CLASS

Summary of the CLASS Trial
Comparison of LAser, Surgery and foam Sclerotherapy

We are conducting a study to find out which treatment is best for patients who have varicose veins. We understand that you have been referred to the hospital about your varicose veins. You might be eligible to take part in our study, and we would be grateful if you would consider taking part.

In our study, we are comparing three different treatments. All of the treatments get rid of varicose veins in the short term but have their own advantages and disadvantages.

In our study, we will compare how well each treatment works in getting rid of varicose veins and in improving the quality of life of patients. We will also look at the recovery and side effects of the treatments and their "value for money".

Standard surgical treatment - removal of the veins under general anaesthetic

Laser treatment - laser treatment to the veins which causes them to close off and shrivel up

Foam sclerotherapy - injections into the veins which causes them to close off and shrivel up

We are inviting patients to take part in this study. Patients who agree will:

- be asked to sign a consent form;
- be allocated to receive one of these treatments by chance;
- have the treatment they have been allocated to;
- be asked to complete questionnaires when they join the study, six weeks after their treatment, six months after their treatment and then every year for five years
- be invited to a follow-up clinic visit six weeks, six months and five years after their treatment (travel expenses will be available to cover the cost of coming to these appointments).

By taking part in the study, patients will give up the right to choose which treatment they receive.

If you are interested in finding out more about the study, the surgeon will tell you about it when you come to your hospital appointment. At this appointment we will give you an information leaflet about the study and one about varicose veins and the different treatments. In the meantime, you can call us on the number above if you would like any more information sent to you.

If you do not want to take part in the study, please tell the surgeon when you come to your hospital appointment.

Thank you

Patients and doctors rely increasingly on the results of studies like this to make sure they are making the right decisions about treatment.

Thank you for reading this leaflet. We hope it was useful in helping you to decide whether or not you would like to help us by participating in this study.

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Comparison of LAser, Surgery and foam Sclerotherapy

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- Invited to a follow-up clinic visit six weeks, six months and five years after their treatment (travel expenses will be available to cover the cost of coming to these appointments).

By taking part in the study, patients will give up the right to choose which treatment they receive. They will be told which treatment they have been allocated to receive about two weeks before their treatment.

You can read more about varicose veins, the different treatments, and about this study in the patient information leaflets.

Thank you

Patients and doctors rely increasingly on the results of studies like this to make sure they are making the right decisions about treatment.

Thank you for reading this leaflet. We hope it was useful in helping you to decide whether or not you would like to help us by participating in this study.

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

PATIENT STUDY INFORMATION LEAFLET

BOOKLET 1

You are invited to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve for you. Please take the time to read this information leaflet carefully and discuss it with others, if you wish. Please ask us if there is anything that is not clear, or if you would like more information. Take as much time as you need to decide whether or not you want to take part.

PART 1

What is the purpose of the study? The purpose of this study is to find out which treatment is best for patients who have varicose veins. We will do this by treating patients who agree to take part with either the standard treatment that is surgery, or alternatively newer treatments which are foam sclerotherapy alone or laser treatment and foam sclerotherapy. These treatments are described below and in more detail in the leaflet "Varicose veins and treatment" which you have been given. We will compare the treatments to find out which is better for getting rid of varicose veins and improving your general health and well-being (quality of life). Patients will be allocated by chance to one of the treatments using a process which is similar to tossing a coin.

More about varicose veins: Varicose veins are veins under the skin of the legs that have become widened, bulging and twisted. They are very common and do not cause medical problems in most people. They may cause aching, discomfort, and heaviness of the legs, which are usually worse at the end of the day. Sometimes the ankle can swell, too. Varicose veins in some cases may occasionally become red and painful or bleed. In a few patients they may lead to skin rashes, a brown discolouration of the skin around the ankle or a break in the skin.

More about standard surgical treatment: This involves removal of the varicose veins under a general anaesthetic. A small cut is then made in the crease of the groin or behind the knee. The main vein is tied off just where it joins the deep vein. This vein is removed by passing a fine wire down it and removed through a small incision further down the leg. Varicose veins marked before the operation are removed through tiny cuts.

Possible advantages and disadvantages of standard surgery

- Standard surgery removes all the varicose veins at a single procedure. It should not be necessary to have anything more done to get rid of any remaining varicose veins.
- Varicose vein surgery is normally done under a general anaesthetic.
- Bruising is common. People with smaller varicose veins may get very little bruising but people with big varicose veins may be very bruised. All the bruising goes away.
- There may be some discomfort from the groin wound and occasionally the groin wound can become infected.
- You can become fully active as quickly as you want after standard surgery.
- Most surgeons advise wearing a support stocking for 10 days and avoiding getting the legs wet (in a bath or shower) during this time.
- Standard surgery gives a good long term result to many people but varicose veins may gradually reappear over the years.
- It is a tried and tested treatment which has been used for many years.
- In summary, surgical treatment involves a general anaesthetic, an incision in the groin or knee and often some bruising. However, all the varicose veins can be dealt with thoroughly by a single treatment, in one or both legs.

More about foam sclerotherapy: This involves injection of a fluid "sclerosant" which is mixed with a small quantity of air in the form of tiny bubbles. This causes the walls of the vein to glue together so that they close off and shrivel up. Foam sclerotherapy involves a number of injections into the veins of the leg and is done under local anaesthetic. These injections are carried out with the help of ultrasound pictures to be sure that the tip of the needle is correctly positioned in the vein. More than one treatment session may be required, particularly for varicose veins on both legs and veins which are very extensive.

Possible advantages and disadvantages of foam sclerotherapy

- Foam sclerotherapy is done under local anaesthetic, but sometimes no anaesthetic is required at all.
- No surgical incisions are required.

- The veins which have been treated may remain lumpy, hard and sometimes tender for several weeks or even months.
- More than one treatment session may be required, particularly for varicose veins on both legs and for veins which are very extensive.
- You can become fully active as quickly as you want after foam sclerotherapy treatment.
- Bandages and a support stocking are put on the leg after foam sclerotherapy treatment, and need to be worn for 10 days. These must be kept dry.
- Varicose veins may gradually reappear in the years after foam sclerotherapy treatment: this is rather more likely than after surgery. They can be treated with further foam sclerotherapy if required.
- In summary, foam sclerotherapy is a simple treatment to have but firm compression from a support stocking is important afterwards. The treated veins may be hard and tender for some time and there may be some brown staining. Repeat treatment sessions may be needed, particularly if there are varicose veins in both legs. New veins may gradually appear.

More about laser treatment: Laser treatment uses heat to damage the walls of the vein causing them to glue together so that they close off and shrivel up. Using ultrasound pictures a special laser fibre is inserted into the vein through a tiny incision near the knee and is advanced up to the top of the vein in the groin. Local anaesthetic and cold fluid are injected around the vein. Pulses of laser light are then used to seal off the vein. Sometimes we may need to use a combination of laser treatment in the thigh and foam sclerotherapy around the knee or upper calf. If required, this will be done at the same treatment session. The veins further down the leg often shrink after laser treatment, but if they persist they can be treated by foam sclerotherapy. One hospital in this study will use phlebectomies (removal of varicose veins through tiny incisions) at the same time as laser treatment.

Possible advantages and disadvantages of laser treatment

- Laser treatment can be done under local anaesthetic, rather than general anaesthetic.
- No incision is needed in the groin.
- It avoids the bruising which can sometimes occur after standard surgery, but you may experience some lumpiness and tenderness in the thigh which can take several weeks to settle.
- Foam sclerotherapy or phlebectomies may be required to get rid of all the varicose veins. This may mean returning for treatment on another occasion.
- You can become fully active as quickly as you want after laser treatment.
- Most surgeons advise wearing a support stocking for 10 days and avoiding getting the legs wet (in a bath or shower).
- Laser treatment seems to give results as good as standard surgery up to five years but varicose veins may gradually reappear over the years.
- In summary, laser treatment can be done under local anaesthetic, requiring several injections into the thigh. Additional treatment may be needed to get rid of all the varicose veins.

Have any studies like this been done before? Yes, there are a number of studies that have shown that either foam sclerotherapy or laser treatment can get rid of varicose veins. However, these studies have not involved all three treatments and did not assess how well each treatment worked in the long-term. Currently we do not know what is the best treatment in terms of getting rid of veins, quality of life and value for money.

Why have I been chosen? You have been chosen because we believe that you are suitable for this study. You have varicose veins which may be treated by surgery, foam sclerotherapy or laser treatment.

Do I have to take part? No. It is entirely up to you to decide whether or not to take part. If you do decide to take part, please keep this information leaflet and the one on “Varicose veins and treatment”. You will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part? If you agree to take part in the study, the study nurse will contact you by telephone in order to arrange a clinic appointment. At this appointment, you will undergo an ultrasound scan of your veins if you have not already had one. This scan involves placing jelly and a probe over the vein. It is painless and lasts up to 20 minutes. You will then be asked to sign a consent form and fill in a questionnaire. The nurse will be available to help with any queries you may have. If there is not enough time at the clinic or if you would prefer, you can complete the questionnaire at home.

You will undergo treatment of your varicose veins by either standard surgery, foam sclerotherapy or laser treatment usually within 4 months. You will be informed of what treatment you are due to receive and the date of this treatment at least two weeks before you are due to attend. At this stage you will be asked to fill in a short questionnaire which will be sent to your home. This questionnaire will let us know if your views on your varicose veins have changed since you agreed to take part in the study.

You will have 2 further clinical visits to the hospital clinic at 6 weeks and 6 months after treatment. You can receive travel expenses. At the clinic you will undergo an examination of your legs, an ultrasound scan and be asked to fill in a questionnaire. The nurse will be available to help with any queries you may have. Each clinic visit should take approximately 1 hour. If you require further treatment with foam sclerotherapy to any remaining varicose veins this will be carried out whenever possible at the same clinic appointment by a doctor.

We are seeking further funding to continue the study to 5 years following your treatment. Assuming we are successful, we will ask you to fill out a questionnaire each year. These will be sent to you by post. At 5 years following your treatment for varicose veins we will ask you to attend a clinic appointment in order to undergo an examination of your leg and an ultrasound scan.

If you agree to take part we will also ask for your permission to consult your medical records. This ensures that the information about you is correctly recorded in the study documentation.

What will I have to do? You will be asked to attend clinic appointments as described above. Your varicose veins will be treated using either standard surgical treatment, foam sclerotherapy or laser treatment.

What is the drug, device or procedure that is being tested? Foam sclerotherapy and laser treatment are being compared with standard surgery. Both of these new treatments are being increasingly used in the NHS and are approved by the National Institute for Health and Clinical Excellence (NICE).

What are the possible disadvantages and risks of taking part? By taking part in the study you will give up your right to choose which treatment you receive. You will be allocated to receive one of the treatments by chance. You will also be given less notice of which treatment you will undergo. We will tell you which treatment you are due to receive about two weeks before your treatment. Your treatment however will not be delayed by your decision to take part in the study. There is a common waiting list for all patients with varicose veins whether they are taking part in the study or not.

There are potential disadvantages/risks of all three treatments. All three treatments for varicose veins are associated with a low risk of developing a clot in the deep veins of the leg known as a deep vein thrombosis. Rarely, a clot like this may break up and travel to the lungs. Varicose veins may come back in the future. The main risks of each treatment are summarised below. For more details please read the leaflet on “Varicose veins and treatment”. This gives information on rare but important complications that may occur.

Surgery: You may experience discomfort following surgery. It is common for the area under the wound in the groin or behind the knee to feel tender for a few days and thickened for a few weeks. Bruising is common, and will settle. Infection is an occasional problem,

particularly in groin wounds. The scars on your legs are easily noticeable to start with, but will continue to fade for many months after the operation. Very occasionally, some people develop a little brown staining where the veins were removed, or the appearance of tiny red or blue veins. Nerves under the skin can be damaged when removing varicose veins close to them and small areas of numbness are quite common. The risk of a deep vein thrombosis following surgery is about 1% (1 in 100). Very rarely the main artery, vein or nerve in your leg may be damaged.

Many people develop a few new varicose veins during the years after a varicose vein operation. Five years after operation about one person in eight has troublesome varicose veins again.

Foam sclerotherapy: You may experience discomfort following the injection of foam. The veins which have been treated may remain lumpy, hard and sometimes tender for several weeks. Skin staining over the veins may occur but will fade with time. Rarely, the skin at the injection site may break down and require treatment. Very occasionally, some people develop tiny red or blue veins. The risk of a deep vein thrombosis following foam injections is about 1% (1 in 100). Some patients experience some temporary confusion after foam treatment – but this generally lasts only a few minutes. There is a small risk that you may experience a brief (about 30 minutes) period of disturbed vision (blurred vision or loss of vision) – the risk is 1% (1 in 100), no permanent damage to eye sight has been reported. Occasionally, people report headache, or migraine-like symptoms after foam sclerotherapy. There is a very small risk of a stroke following foam treatment. All the surgeons involved in this study take care to limit the amount of foam that is used at any one time and this minimises the risk. That is the reason that we often treat only one leg at a time, even if both legs are to be treated. Worldwide, three patients have been reported as having foam injected into an artery rather than a vein. One patient has had a fit following foam, but it is unclear if this was related to the treatment. A severe allergic reaction known as anaphylaxis may rarely occur.

More than one treatment session may be required, particularly for varicose veins on both legs and veins which are very extensive. Bandages and a support stocking are put on the leg after foam sclerotherapy treatment and need to be worn for 10 days. These must be kept dry. Many people develop a few new varicose veins during the years after a foam sclerotherapy. There have not been enough scientific reports on the long term results of foam sclerotherapy to give precise figures.

Laser treatment: You may experience discomfort following laser treatment. You may experience some lumpiness and tenderness in the thigh/back of leg which can take several weeks to settle. You may also get patches of numbness over the vein which will disappear with time. The risk of a deep vein thrombosis following laser treatment is about 1% (1 in 100). Very occasionally, laser treatment can damage the main vein in the leg. Additional treatment in the form of foam sclerotherapy may be required to get rid of all the varicose veins. This may mean returning for treatment on another occasion. Most surgeons advise wearing a support stocking for about 10 days and avoiding getting the legs wet (in a bath or shower) for the 10 days. Many people develop a few new varicose veins during the years after a laser treatment. There have not been enough scientific reports on the long term results of laser treatment to give precise figures.

What are the possible benefits of taking part? We hope that the results from the study may benefit people with varicose veins in the future and will help us recommend the best type of treatment. If you are allocated foam sclerotherapy or laser treatment then you will avoid a general anaesthetic, a groin incision and bruising. But unlike surgery you may need to attend for more than one treatment session. The long term results of surgery are well known but there is much less information available for foam sclerotherapy and laser treatment. After all three treatment options you can become fully active as quickly as you want.

What happens when the research study stops? You will be followed up in the usual way.

What if there is a problem? Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed (see part 2 of this leaflet).

Will my taking part be confidential? Yes. All the information about your participation in this study will be kept confidential. The details are included in part 2 of this leaflet.

PART 2

What if new treatment becomes available? If a new treatment or information becomes available during the study, you will be made aware of this and you may decide whether or not to continue in the study. You may decide this at any time and your decision will not affect the long-term care you receive in the hospital. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your doctor might consider it to be in your best interest to withdraw from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any reason you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with this study? You can withdraw from the study at any time, but, you should keep attending the hospital to have your varicose veins treated.

What if there is a problem? If you have a concern about any aspect of the study, you should ask to speak with the researchers who will do their best to answer your questions (contact details on page 12 of this leaflet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints procedure. Details can be obtained from the hospital.

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspects of this study, the normal National Health Service mechanisms may be available to you.

Will my taking part in the study be kept confidential? All information that is collected about you during the course of the research will be kept strictly confidential. Personal data from all study participants will be collected and stored at the CLASS Trial Office in Aberdeen. By consenting to take part in this study, you are agreeing that your medical records and data collected during the study may be looked at by individuals directly involved in the trial, from regulatory authorities, from the University of Aberdeen or from the NHS Boards or Trusts, where it is relevant to your taking part in this research. The purpose of this review of your medical records is to ensure that the information about you is correctly recorded in the study documentation. You should be aware that all records of your participation in the study will be handled, stored and destroyed in compliance with the Data Protection Act of 1998.

Will any genetic tests be done? No.

What will happen to the results of the study? When the study is finished all the results will be analysed and the results may be published in a medical journal (while maintaining confidentiality of your identity) and presented at scientific meetings. We will send out a study newsletter every 6 months to keep you updated on the progress of the study.

Who is organising and funding this study? This study is being funded by the NHS National Institute for Health Research Health Technology Assessment programme. The study has been designed by UK vascular surgeons and researchers. Patients will be recruited at different hospitals in England and Scotland. It is being coordinated by the Centre for Healthcare Randomised Trials (CHaRT) located in the Health Services Research Unit at the University of Aberdeen, Scotland.

Will my doctor be paid for including me? The doctor conducting the research will not be paid for including you in the study or looking after you during the course of the study.

Will my own GP know that I am taking part in this study? With your consent, we will inform your GP that you are taking part in the study. We will also ask for your permission to record the name and address of a family member or friend who we could contact if we have

difficulty getting in touch with you during the planned five year follow up period (for example if you moved house). We call this your "best contact". Please tell them that you have nominated them as your "best contact".

Who has reviewed the study? This Study has been approved by the Main Research Ethics Committee and Local Research Ethics Committee. The study also is registered and approved by the Medicines and Healthcare products Regulatory Agency (MHRA).

Who can I contact for more information?

[Local recruitment contact details]

Thank you

Patients and doctors rely increasingly on the results of Clinical Trials like the CLASS trial to make sure that they are making the right decisions about treatment. Thank you for taking the trouble to read this information leaflet, we hope that it will have been helpful in enabling you to decide whether or not you would like to help us by participating in this study.

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

VARICOSE VEINS AND TREATMENTS INFORMATION FOR PATIENTS

BOOKLET 2

We are performing a research study which compares three different treatments for varicose veins: foam sclerotherapy, laser treatment or standard surgery. You will have been provided with the patient study information leaflet on this study (booklet 1). We know that each of the treatments do get rid of varicose veins in the short-term, but they have different advantages and disadvantages. The trial compares how well each treatment works in getting rid of varicose veins and in improving quality of life. It also compares the recovery and the side effects of the different treatments. In addition, the trial will compare the "value for money" of the treatments (that is, how much it costs to give a particular amount of improvement to the quality of people's lives).

Information in this leaflet is divided into these sections:

1. Information about varicose veins and the problems they can cause.

2. A detailed description of:
   - What happens at the time of each treatment
   - The possible problems and side effects which can occur
   - Advice about the recovery and return to activity after treatment

3. A summary of the possible advantages and disadvantages for each treatment.

For more information, please contact:

[Local recruitment contact details]

Section 1. Information about varicose veins and the problems they can cause.

What are varicose veins?

Varicose veins are veins under the skin of the legs which have become widened, bulging and twisted. They are very common and do not cause medical problems in most people.

Blood flows down the legs through the arteries, and back up the legs through the veins. There are two main systems of veins in the legs - the deep veins which carry most of the blood back up the legs to the heart, and the veins under the skin, which are less important and which can form varicose veins. All these veins contain valves which should only allow the blood to flow upwards. If the veins become widened and varicose these valves no longer work properly. Blood can then flow backwards down the veins and produce a head of pressure when standing, walking about, or sitting. Lying down or "putting your feet up" relieves this head of pressure and usually makes the legs feel better. Both symptoms and treatment depend on how badly the valves in the veins are working, although the inconvenience people get from their varicose veins is very variable.

What problems can varicose veins cause?

Very many people have no symptoms at all from their varicose veins, except for the fact that they are noticeable, and their appearance can be embarrassing. Simply having varicose veins is not a good reason for having treatment. Other than cosmetic embarrassment the common symptoms of varicose veins are aching, discomfort, and heaviness of the legs, which are usually worse at the end of the day. Sometimes the ankle can swell, too. These symptoms are not medically serious, but can be treated if they are sufficiently troublesome. Although varicose veins can get worse over the years, this often happens very slowly and worry that "they might get worse" is not a good reason for treatment if the veins are not causing symptoms.

In a few people the high pressure in the veins causes damage to the skin near the ankle, which can become brown in colour, sometimes with scarred white areas. Eczema (a red skin rash) can develop. If these changes are allowed to progress, or if the skin is injured, an ulcer may result. Skin changes are therefore a good reason for going to see your GP and for referral to a specialist.

Other problems which varicose veins can occasionally produce are phlebitis and bleeding. Phlebitis (sometimes called thrombophlebitis) means inflammation of the veins, and is often accompanied by some thrombosis (clotting of blood) inside the affected veins, which become hard and tender. This is **not** the same as deep vein thrombosis and is not usually dangerous. It does not mean that the varicose veins necessarily have to be treated. The risk of bleeding as a result of knocking varicose veins worries many people, but this is very rare. It will always stop with firm pressure and the veins can then be treated to remove the risk of further bleeding.

How can varicose veins be treated?

The symptoms of varicose veins can often be improved by wearing support stockings or tights. Compression stockings up to the knee (like “flight socks”) are often prescribed for people with discomfort, swelling or skin trouble. Many people do not get on well with compression stockings because they find them difficult to put on, or they find them hot and uncomfortable.

People who have troublesome symptoms but for whom compression hosiery is not an acceptable long-term solution can have treatment to get rid of their varicose veins.

This trial is comparing three treatments which remove the varicose veins or seal them off so that they shrivel up. These three treatments are described in this leaflet.

Section 2. A detailed description of each treatment, possible problems and side-effects, and advice about recovery and return to activity.

Foam Sclerotherapy - the procedure

How long will I be in hospital for foam treatment? Foam sclerotherapy is done as an outpatient. The arrangements differ from hospital to hospital: sometimes the procedure is done in an outpatient clinic and sometimes in an operating theatre.

What happens before the treatment? When you arrive at the clinic a nurse will meet you and will measure your legs for stockings. The surgeon doing the foam treatment will talk with you about what is going to happen. You need to remove your trousers and socks or stockings for the treatment. It is best not to wear tight trousers as you may have difficulty putting them on over the bandage and stocking afterwards.

What happens during foam sclerotherapy treatment? Foam sclerotherapy involves one or more injections into veins of the leg, which are given while you are lying on a couch. These injections are often carried out with the help of ultrasound pictures to be sure that the tip of the needle is correctly positioned in the vein. If the vein is easy to see and feel then ultrasound may not be required. Depending on the vein being injected and the type of needle used, an injection of local anaesthetic may be given first. Sometimes gaining safe and secure access to a vein may need more than one attempt: it is very important to be sure that foam is not injected outside the vein.

After the needles have been secured in selected veins, the leg is usually elevated before foam is injected. Pressure may be applied to the groin or elsewhere to prevent foam entering deeper veins. Nevertheless, after each injection you will be asked to move the foot up and down at the ankle in order to pump blood through the deeper veins, just in case any foam has entered them – movement of the calf muscles flushes away any small amounts of foam.

Following injection, pads and bandages are applied to the leg, and then a firm stocking. These need to be worn for 10 days. During that time you cannot get the bandaged part of the leg wet in a bath or shower.

Foam sclerotherapy treatment takes about half an hour in total. Keep one hour free in case of delays.

After treatment – leaving hospital. You can get up and walk normally immediately after foam sclerotherapy. It is a good idea to go for a walk for about five minutes after getting dressed, to encourage blood flow through the veins. You can leave the hospital shortly after the treatment. We will arrange a follow-up appointment at about 6 weeks after the procedure.

Foam Sclerotherapy - Recovery

How much does it hurt afterwards? Other than the inconvenience of the bandages and stocking, foam sclerotherapy does not usually cause any immediate discomfort after treatment. The varicose veins become hard, lumpy and tender: this can last for several days, and sometimes persists for weeks, but gradually settles. If the veins are particularly uncomfortable or inflamed, you can take an anti-inflammatory painkiller like ibuprofen (Nurofen). Paracetamol is an alternative, particularly if you have had any gastric acid problems or asthma which prevent you from taking medicines like ibuprofen.

What about the bandages and support stockings? Your bandages and stocking must remain in place for 10 days. After this time you can remove them. Throw away the bandages and padding, but keep the stocking (do wash it) in case you need further treatment.

Showering and bathing. Because of the bandages and stocking, you cannot have a normal bath or shower for 10 days after foam sclerotherapy. A shower may be possible by securing a large plastic bag over the leg or by using a special waterproof cover such as a Limbo waterproof protector (Thesis Technology, Chichester OP18 8AT or on prescription). After the bandages have been removed you can shower or bath normally.

Activity. **Aim to get back to all your normal activities just as soon as you are able**. The ***only*** special restriction is bathing and showering, which you cannot do normally for 10 days (see above). The only limitation to your activity might be discomfort and tenderness (which can be minimised by taking painkillers) and the need to wear the bandaging and stocking.

Walking. You should start to walk about as soon after foam sclerotherapy as you are able. You can walk as much as you want, as soon as you want. Your thigh may be uncomfortable and tender to the touch in places. You will not cause any damage by walking. Take painkillers if you need them.

There is *no* special advantage in going for a single long walk during the day, although you may walk as far as you wish. Frequent walking is more important than walking a long distance.

Standing and sitting. During the first week after foam sclerotherapy, try to avoid prolonged standing, or sitting with the foot on the floor continuously for longer than about half an hour at a time. Every half hour or so, go for a short walk about or do a few “tip-toe” exercises. If you are sitting or resting for any length of time try to put your foot up - either on a stool or couch or on your bed.

When can I return to work and play sports?

Work. This varies a lot between different people. Most people are able to return to work within two or three days after the treatment. Some people go back to work the following day or even the same day.

Sports. You can return to work and sporting activity as soon after foam sclerotherapy as you feel sufficiently comfortable. Avoid contact sports while you are still in support stockings or bandages, and thereafter start with some gradual training, rather than in immediate competition. Do not go swimming until your bandage has been removed.

Driving. You can drive as soon as you feel confident that you can make an emergency stop safely: practise this before you drive. We would advise you not to drive yourself home following foam sclerotherapy but other than that you can drive as soon as you feel able.

Air travel. The risk of deep vein thrombosis during long air flights or other long journeys in cramped seating is very low, but it is probably best to avoid this kind of travel for about a month after foam sclerotherapy.

Foam Sclerotherapy - risks

What problems can occur after foam sclerotherapy?

Inflammation. The injected veins may be somewhat inflamed and hard for a few days (like phlebitis). This is because the foam sclerotherapy works by causing some inflammation of

the vein walls, which helps them glue together. Occasionally inflammation can be more severe and painful. If this occurs then an anti-inflammatory painkiller such as ibuprofen (Nurofen) will help to settle the symptoms.

Lumpiness and hardness. The injected veins sometimes remain lumpy and hard for many weeks after treatment, but they gradually shrivel.

Damage to skin. Rarely, the skin at the injection site may break down and require treatment.

Bruising and discolouration. A little bruising may occur after foam sclerotherapy. In some people, brownish discolouration of the skin occurs in the areas where the veins were. Usually this fades, but occasionally discolouration may persist: this is more noticeable in people with naturally pale skin.

Thread veins. Any kind of sclerotherapy can occasionally be followed by the appearance of tiny red or blue veins in the area which was injected. This is uncommon.

Headache/migraine-like symptoms. Occasionally, people report headache, or migraine-like symptoms after foam sclerotherapy. It is thought that these are more common in people who have experienced frequent or severe migraines in the past. For this reason, in this study, we do not treat people with foam sclerotherapy if they have had frequent or severe migraines in the past.

Deep vein thrombosis (DVT). Deep vein thrombosis causes swelling of the leg and can result in a blood clot passing to the lungs. It is a possible complication after varicose vein surgery, but the risk is considerably reduced if you start moving your legs and walking frequently soon after the operation. Sometimes, injections are given so that blood clots less than normal: this reduces the risk of thrombosis but increases bruising. The risk of DVT is about 1% (1 in 100 patients). Rarely, a clot like this may break up and travel to the lungs.

Injection into the artery. Many thousands of patients have been treated with foam sclerotherapy. Among these, there have been three reported cases of foam being injected into an artery rather than a varicose vein.

Concern about stroke and loss of vision. This has been a cause for concern, but there is no good evidence that it is a real risk when normal amounts of foam are used. The reasons for the concerns have been:

- There is a possibility that small amounts of foam could circulate in the blood stream, and, in particular, they could pass through small ‘holes in the heart’ which are present in some otherwise fit people. Theoretically this could allow foam to pass to small blood vessels – for example those in the eye or brain.
- Some patients have reported temporary disturbance of vision (i.e. blurred vision or loss of vision) after foam sclerotherapy. The risk of this happening is about 1% (1 in 100). There has been concern that any disturbance of vision might be due to tiny bubbles entering small blood vessels in the back of the eye. The very few patients in whom this has been reported have all rapidly recovered their full vision, generally within 30 minutes. The worry that air bubbles might cause permanent loss of vision is a theoretical one: it has not been reported as having happened.
- Stroke and mini-stroke (transient ischemic attack) have been described in a very few patients worldwide. One case of stroke was in a patient in whom a large volume of foam was used (much larger than is now recommended). All the surgeons involved in this study limit the amount of foam that is used at any one time and this minimises the risk of stroke.

Temporary confusion: Among the thousands of patients that have been treated throughout the world with foam, a few patients have experienced some temporary confusion after the treatment. Any confusion is likely to be very short-term (lasting only a few minutes).

Concern about fit. One patient has had a fit following foam, but it is unclear if this was related to the foam treatment.

Anaphylaxis/Allergic reaction. This is rare and may cause a rash and a fall in your blood pressure. In extreme cases you may lose consciousness. In the unlikely event that this may occur, equipment and the necessary drugs will be available to enable the doctor and nurse to treat you immediately.

Varicose veins coming back.
Many people develop a few new varicose veins during the years after foam sclerotherapy. There have not been enough scientific reports on the long term results of foam sclerotherapy to give precise figures. Varicose veins may simply re-grow in the areas which have been dealt with, or they may develop in different veins which were normal at the time of the original treatment. If veins develop again they can be treated.

Laser only or laser plus foam sclerotherapy - Procedure

Laser treatment is used to seal off the main vein under the skin in the thigh or the calf. This takes away the head of pressure which causes varicose veins to bulge and cause symptoms. Sometimes we need to use a combination of laser treatment in the thigh and foam sclerotherapy of the main vein at the knee or upper calf. If required, this will be done at the same treatment session.

Laser treatment alone may cause the varicose veins to disappear or reduce in size, but if visible varicose veins remain after the laser treatment, you may wish to have them treated by foam sclerotherapy. Foam sclerotherapy may be done at one or more later treatment sessions. One hospital in the study uses phlebectomies (removal of veins through tiny incisions) at the same time as laser treatment.

How long will I be in hospital for laser treatment? You will have your treatment performed as an outpatient. The procedure itself takes about 45 minutes. You will be in the hospital for about 2 hours in total, but you should keep half a day free in case of delays.

What happens before the treatment? When you arrive a nurse will meet you and will measure your legs for stockings and show you where to get changed. It is best not to wear tight trousers as you may have difficulty putting them on over the stocking afterwards.

The consultant or a member of the surgical team will talk with you about what is going to happen and will mark your varicose veins with a felt tip pen.

What happens during laser treatment? An injection of local anaesthetic is given to freeze the skin just above, or just below, the knee or in the calf. Once the skin is numb a needle is inserted into a vein beside the knee. A wire is then passed up the vein to the groin and the laser filament is passed over the wire. You will not feel this. The position of the laser filament is checked using an ultrasound scanner. The area around the vein and the skin is then made numb using cold local anaesthetic injections from the knee to the groin. This usually requires 4 or 5 injections with a small needle.

The laser is fired as it is gradually pulled back down the vein from the groin to the knee. This should not be painful because of the local anaesthetic, but you may feel some pushing, pulling or mild discomfort during the procedure. If you feel anything more than this you should say so: the procedure can then be temporarily stopped to settle this.

The heat from the laser closes (cauterises) the vein from the inside. Lasers are powerful sources of energy and you and all the staff will wear protective goggles during the time that the laser is working.

When the vein has been sealed up, the laser is removed from the leg and a firm stocking is applied. This needs to be worn for 10 days. During that time you cannot get the stocking wet in a bath or shower.

After treatment – leaving hospital. Immediately following the procedure, once you have got dressed, you should go for a 10 minute walk. Once you have been for a walk we will offer you a cup of tea and you are then free to go home.

We will arrange a check up for you about 6 weeks after the procedure. By that time most of the varicose veins in your leg should have shrunk and many, or all of them may have disappeared. If there are any left they can be treated by foam sclerotherapy.

Laser - Recovery

How much does it hurt afterwards? You may experience some discomfort or pulling on the inside of your thigh following the treatment. This may be most noticeable for about one week after treatment, but it then settles down.

People vary a lot in the amount of pain they experience after laser treatment, though most experience discomfort only. You will be encouraged to get up and walk immediately following the laser treatment.

You will be given a supply of an anti-inflammatory drug, such as ibuprofen (Nurofen) or diclofenac (Voltarol) which are also painkillers. We recommend that you take these regularly for three days. If you have had a stomach ulcer, or asthma then you should not take anti-inflammatory drugs of this kind: tell us and we will supply you with a painkiller which suits you.

If any discomfort occurs after three days, take a simple painkiller such as paracetamol (Panadol).

What about my wound? The small cut beside your knee where the laser fibre was inserted is closed with an adhesive strip. It can be removed when your stocking is removed.

What about the bandages and support stockings? Your stocking must remain in place for 10 days after which time you can remove it. Do not get the stocking wet during these 10 days. Please keep the stocking (do wash it) in case you need further treatment.

Bathing and showering. Because of the stocking, you cannot have a normal bath or shower until 10 days after laser treatment. A shower may be possible by securing a large plastic bag over the leg or by using a special waterproof cover such as a Limbo waterproof protector (Thesis Technology, Chichester OP18 8AT or on prescription).

What should I expect my leg to be like after laser treatment? You may be aware of areas of lumpiness on the leg which may be slightly tender. This is caused by some inflammation in the vein that has been treated. It is not harmful and will gradually go away, but this may take several weeks. The inner side of your thigh may be uncomfortable during the first few days.

Activity. **Aim to get back to all your normal activities just as soon as you are able**. The ***only*** special restriction is bathing and showering, which you cannot do normally for 10 days (see above). The only limitation to your activity might be discomfort and tenderness (which can be minimised by taking painkillers) and the need to wear the stocking.

Walking. You should start to walk about as soon after laser treatment as you are able. You can walk as much as you want, as soon as you want. Your thigh may be uncomfortable and tender to the touch in places. You will not cause any damage by walking. Take painkillers if you need them.

There is *no* special advantage in going for a single long walk during the day, although you may walk as far as you wish. Frequent walking is more important than walking a long distance.

Standing and sitting. During the first week after laser treatment, try to avoid prolonged standing, or sitting with the foot on the floor continuously for longer than about half an hour at a time: go for a short walk about or do a few "tip-toe" exercises. If you are sitting or resting for any length of time try to put your foot up - either on a stool or couch or on your bed.

When can I return to work and play sports?

Work. This varies a lot between different people. Most people are able to return to work within two or three days after the treatment – some people go back the following day or even the same day.

Sports. You can return to work and sporting activity as soon after treatment as you feel sufficiently well and comfortable. Avoid contact sports while you are still in support stockings or bandages, and thereafter start with some gradual training, rather than in immediate competition. Do not go swimming until your bandage has been removed. We suggest avoiding strenuous activity like the gym for about 2 weeks after the procedure.

Driving. You can drive as soon as you feel confident that you can make an emergency stop safely: practise this before you drive. We would advise you not to drive yourself home following the laser treatment, but other than that you can drive as soon as you feel able.

Air travel. The risk of deep vein thrombosis during long air flights or other long journeys in cramped seating is very low, but it is probably best to avoid this kind of travel for about a month after your treatment.

Laser - risks

What problems can occur after the laser treatment?

Bruising. Some bruising is normal, and occasionally the leg becomes very bruised. This bruising appears during the first few days after laser treatment: it will all go away over a period of weeks.

Aches, twinges, and areas of tenderness may all be felt in the legs for the first few days after the laser treatment. These will settle down, and should not discourage you from becoming fully active as soon as you are able.

Tender lumps under the skin are common and are caused by blood clots that have collected in the places where the vein has been treated. They are not dangerous and will gradually disappear. It may take up to 12 weeks for all the lumps to disappear. Occasionally they can be quite painful during the first two weeks or so.

Numbness. Areas of numbness in the skin can occasionally occur at the places where varicose veins were treated. This is because tiny nerves may be damaged by heat from the laser. This will not affect the movement of your foot or your walking. The numbness will usually recover over a period of several weeks.

Thread veins. Laser treatment can occasionally be followed by the appearance of tiny red or blue veins in the area which was injected. This is uncommon.

Deep vein thrombosis (DVT). Deep vein thrombosis causes swelling of the leg and can result in a blood clot passing to the lungs. It is a possible complication after varicose vein surgery, but the risk is considerably reduced if you start moving your legs and walking frequently soon after the operation. Sometimes, injections are given so that blood clots less than normal: this reduces the risk of thrombosis but increases bruising. The risk of DVT is about 1% (1 in 100 patients). Rarely, a clot like this may break up and travel to the lungs.

Damage to major vein. Damage to the major veins in the leg is a rare complication of laser treatment, which we take great pains to avoid.

The risks of additional foam sclerotherapy. Remember that you may require foam sclerotherapy, in addition to laser treatment, to get rid of all your varicose veins.

Will varicose veins come back? Many people develop a few new varicose veins during the years after laser treatment. There have not been enough scientific reports on the long term results of laser treatment to give precise figures. Varicose veins may simply re-grow in the areas which have been dealt with, or they may develop in different veins which were normal at the time of the original treatment. If veins develop again they can be treated.

Surgery - procedure

How long will I be in hospital for surgery? If you are medically fit and have somebody at home with you then a day case operation is usual. If you have medical conditions, if you live some distance away or if you are having surgery for extensive varicose veins in both legs, then you may have your operation as an in-patient (you may be admitted the day before your operation for the doctors and nurses to assess your needs; or on the morning of the operation, and then stay overnight).

What happens before the treatment? A member of the surgical team will check that all the necessary preparations have been made and will mark your varicose veins with a felt tip pen. Be sure that all the veins you would like dealt with have been marked, and ask about any which have not.

Shaving may be done before your operation or in the operating theatre. If you are going to have an incision in the groin, this area will need to be shaved, but there will be no need to shave all the pubic hair. The leg will need to be shaved, at least in the areas of the varicose veins which are going to be removed. This makes marking of your varicose veins easier and means that hairs do not get into the wounds during the operation.

What happens during surgery? Surgery is usually done under a general anaesthetic. An incision (2 – 4 cm long) is made over the top of the main vein in the crease of the groin or behind the knee. It is tied off just where it joins the deep vein, so relieving the “head of pressure” on the varicose veins further down the leg. This incision is closed with stitches, which are hidden under the skin.

The vein is removed by passing a fine wire down it and making a small incision (less than 1 cm long) near the knee – “stripping”. This helps to guard against varicose veins forming

again. Blood flows up the many other veins in the leg after this vein has been removed and it is therefore safe to remove this vein.

Varicose veins marked before the operation are removed through tiny cuts ("phlebectomies"). These cuts can be closed with stitches or adhesive strips.

After treatment – leaving hospital. You can get up and walk about as soon as the effects of the anaesthetic have worn off, shortly after the operation. If you are being treated as a day case, after two or three hours you should feel fit enough to go home. Before you leave the hospital staff will check your leg. They will give you a note for your GP, and some painkillers to take with you. They will make arrangements for you to visit a practice nurse the next day (or if necessary for a nurse to call) to check on you and change your bandages for a support stocking.

If you are treated as an inpatient, the bandages on your leg/s will be changed on the morning after your operation for a support stocking. You will normally be able to go home shortly afterwards.

Surgery - recovery

How much does it hurt afterwards? We inject a long acting local anaesthetic into the groin wound at the end of the operation. This is usually the most uncomfortable area. People vary a lot in the amount of pain they experience after the operation, though most experience mild discomfort only. It is more uncomfortable to get up and walk after operation to both legs than when only one leg has been dealt with. In either case you will be encouraged to get up and walk on the day of your operation when the effects of the anaesthetic have worn off sufficiently.

Painkillers such as paracetamol or anti-inflammatory painkillers like ibuprofen (Nurofen) or diclofenac (Voltarol) will be prescribed for you to take after the operation. It is important that you should take these if you need them to walk about and to rest with comfort. You should not need them for more than a few days, but the duration of discomfort varies from person to person. Occasionally tender lumps of old blood clot (haematoma) beneath the skin can become inflamed and very tender. This is not infection, but you may require to take anti-inflammatory drugs for a longer period.

Will I have dressings or stitches? Stitches are placed under the skin in the groin and do not have to be removed. If the surgeon has used a dressing on the groin, this can be removed after 48 hours. The groin wound can be washed and gently dried from 48 hours after the operation, to keep the area fresh and clean.

The small incisions further down the leg are closed with adhesive strips and it is best to keep these dry for 10 days. 10 days after the operation you can remove the strips yourself: this is often easiest in the bath or shower which helps to loosen them. After that time there is no restriction at all in taking a shower or bath.

What should I expect my leg to be like after surgery? Bruising is common after varicose vein operations. It is sometimes quite extensive and may take a month or more to settle. In particular it can occur on the inner side of the thigh, where may be no incisions. This is caused by removing the main vein under the skin from this area. Hard lumps are also common – they represent bruising in places where the varicose veins used to be. Any bruising and lumpiness may be tender but you will do no harm by becoming active. Take painkillers if you need them.

What about bandages and support stockings? Your bandages will be changed for support stocking/s the day after operation. Wear these for 10 days after the operation. There is no need to wear the stockings after removing the adhesive strips 10 days after the operation (but if you feel more comfortable with them for another few days this is quite

alright). If you find the stocking/s uncomfortable or excessively hot, it is reasonable to remove them four or five days after the operation, provided you are easily and frequently active. An alternative is to remove them at night only, and to put them on each day – but some people find it difficult putting them back on. They are mainly intended to support the leg while you are up and about during the day.

Bathing and showering.
Groin wounds: You can wash your groin wound gently after 48 hours, as described above.

Keep all the other wounds dry for 10 days so that they properly heal. At 10 days you can soak the adhesive strips off in a bath or shower.

You cannot have a normal bath or shower until 10 days after the operation. Before 10 days, some people manage a shallow bath by putting their leg up on the side of the bath to keep it dry, if there are no wounds or dressings above the knee. A shower may be possible before 10 days by securing a large plastic bag over the leg or by using a special waterproof cover such as a Limbo waterproof protector (Thesis Technology, Chichester OP18 8AT or on prescription). If any of the adhesive strips do come off early, the little wound beneath it is likely to be quite alright but you can cover it with a plaster (e.g. Bandaid) if you want.

Activity. Aim to get back to all your normal activities just as soon as you are able. The ***only*** special restriction is bathing and showering, which you cannot do normally for 10 days (see above).

The only limitation to your activity should be discomfort and tenderness from bruising which can be minimised by taking painkillers. If you can get back to all the things you would like to do within a few days of the operation, then do so. The time taken to get fully back to all activities varies quite a lot between different people. If you had many large veins then you are more likely to be bruised and tender. Do not let this put you off becoming active: you will do no harm.

Walking. You should start to walk about as soon after the operation as you are able. You can walk as much as you want, as soon as you want. Getting up from a seated position or bed is sometimes a little uncomfortable during the first two or three days after the operation, particularly where the groin or the area behind the knee has been operated on. The whole leg may be stiff, and tender to the touch in places. You will not damage any of the wounds by walking. Take painkillers if you need them.

There is *no* special advantage in going for a single long walk during the day, although you may walk as far as you wish. Frequent walking is more important than walking a long distance.

Standing and sitting. During the first week after surgery, try to avoid prolonged standing, or sitting with the foot on the floor continuously for longer than about half an hour at a time: go for a short walk about or do a few “tip-toe” exercises. If you are sitting or resting for any length of time try to put your foot up - either on a stool or couch or on your bed.

When can I return to work and play sports?

Work. You can return to work as soon after the operation as you feel sufficiently well and comfortable. After an operation on one leg there is no reason to anticipate being away from “office” or sedentary work for more than two or three days. If your job involves prolonged standing (without the opportunity to walk about) or driving, then you should wear the support stocking if you return to work within two weeks of the operation. We hope that people will be back at work within a week after surgery to one leg and two weeks after surgery to both legs – but there is no reason to remain off work that long if you can manage with reasonable comfort.

Sports. Be guided by how your legs feel: bruising and tenderness may limit you from being very active or from some activities in the first few days after the operation, but you can do whatever is comfortable. Avoid very strenuous leg exercise (e.g. running) during the first week, and thereafter it is usually best to start with some gradual training, rather than in immediate competition. Do not go swimming until all the wounds are healed and dry (at least 10 days).

Driving. You should not drive within 24 hours of a general anaesthetic. Thereafter you can drive as soon as you feel confident that you can make an emergency stop without pain: practise this before you drive.

Air travel. The risk of deep vein thrombosis during long air flights or other long journeys in cramped seating is very low, but it is probably best to avoid this kind of travel for about a month after your operation.

Surgery - risks

What problems can occur after surgery?

Discomfort. Aches, twinges, and areas of tenderness may be felt in the legs for the first few weeks. These will settle down, and should not discourage you from becoming fully active as soon as you are able.

Lumps. Tender lumps under the skin are common (especially in the thigh) and are caused by blood clots which have collected in the places where the veins were removed. They are not dangerous and will gradually disappear but this can take several weeks. Occasionally they can be quite painful during the first two weeks or more. It is common for the area under the groin wound to feel tender for a few days and thickened for a few weeks.

Infection. Infection is an occasional problem, particularly in groin wounds. It is more of a risk in people who are overweight and after operation for recurrent varicose veins. Infection usually settles with antibiotic treatment. If the wound was closed by a stitch under the skin, this may need to be removed to allow the infection to clear up. If an abscess forms, this may need to be drained at an operation under general anaesthetic and the wound will then require dressings – sometimes for up to a month.

Scars and blemishes. The scars on your legs are easily noticeable to start with, but will continue to fade for many months after the operation. Very occasionally, some people develop a little brown staining where the veins were removed. Another uncommon but disappointing problem is the appearance of tiny thread veins or “blushes” on the skin in the areas where varicose veins were removed.

Nerve damage. Nerves under the skin can be damaged when removing varicose veins close to them and small areas of numbness are quite common. If a nerve lying alongside one of the main veins under the skin is damaged, then a larger area of numbness can be caused. If this happens after surgery to the main vein on the inner side of the leg, then numbness will result over the inner part of the lower leg and foot. If a main vein behind the knee needs to be dealt with, then there is a risk to the nerve which conducts feeling from the skin on the outer part of the lower leg and foot. Areas of numbness often get better over weeks or months, but sometimes they persist in the long term.

Damage to major structures. Damage to major arteries, veins, and the main nerve which allows the leg to move normally have all happened during varicose vein operations, but are very rare complications (less than 1 in 10,000), which we take great pains to avoid.

Swelling. Damage to the tiny lymphatic vessels which drain tissue fluid from the foot and leg, and which run close to the veins, can occasionally cause problems. Swelling of the foot and ankle can occur, which usually settles over a period of several weeks, but very rarely it

may persist. Tissue fluid may rarely collect under the groin wound, forming a swelling (which usually goes away after a time) or very occasionally tissue fluid may leak from the groin wound. These problems are all more common after operations for recurrent varicose veins.

Deep vein thrombosis (DVT). Deep vein thrombosis causes swelling of the leg and can result in a blood clot passing to the lungs. It is a possible complication after varicose vein surgery, but the risk is considerably reduced if you start moving your legs and walking frequently soon after the operation. Sometimes, injections are given so that blood clots less than normal: this reduces the risk of thrombosis but increases bruising. The risk of DVT is about 1% (1 in 100 patients). Rarely, a clot like this may break up and travel to the lungs.

The risks of a general anaesthetic. Varicose vein operations are almost always done under a general anaesthetic. General anaesthetics have some risks, which may be increased if you have chronic medical conditions, but in general they are as follows:

Common temporary side-effects (risk of 1 in 10 to 1 in 100) include bruising or pain in the area of injections, blurred vision and sickness (these can usually be treated and pass off quickly).

Infrequent complications (risk of 1 in 100 to 1 in 10,000) include temporary breathing difficulties, muscle pains, headaches, damage to teeth, lip or tongue, sore throat and difficulty speaking.

Extremely rare and serious complications (risk of less than 1 in 10,000). These include severe allergic reactions and death, brain damage, kidney and liver failure, lung damage, permanent nerve or blood vessel damage, eye injury, and damage to the voice-box. These are very rare and may depend on whether you have other serious medical conditions.

Varicose veins coming back. Many people develop a few new varicose veins during the years after a varicose vein operation and five years after operation about one person in eight has troublesome varicose veins again. Varicose veins may simply re-grow in the areas which have been dealt with, or they may develop in different veins which were normal at the time of the original operation. If veins develop again they can be dealt with by injections or a further operation should they be troublesome.

Section 3. Summary of the possible advantages and disadvantages for each treatment

Possible advantages and disadvantages of foam sclerotherapy.

- Foam sclerotherapy is done under local anaesthetic, but sometimes no anaesthetic is required at all.
- No surgical incisions are required.
- The veins which have been treated may remain lumpy, hard and sometimes tender for several weeks or even months.
- More than one treatment session may be required, particularly for varicose veins on both legs and for veins which are very extensive.
- You can become fully active as quickly as you want after foam sclerotherapy treatment.
- Bandages and a support stocking are put on the leg after foam sclerotherapy treatment, and need to be worn for about 10 days. These must be kept dry.
- Varicose veins may gradually reappear in the years after foam sclerotherapy treatment: this is rather more likely than after surgery. They can be treated with further foam sclerotherapy if required.
- In summary, foam sclerotherapy is a simple treatment to have but firm compression from support stockings is important afterwards. The treated veins may be hard and tender for some time and there may be some brown staining. Repeat treatment sessions may be needed, particularly if there are varicose veins in both legs. New veins may gradually appear.

Possible advantages and disadvantages of laser treatment.

- Laser treatment can be done under local anaesthetic, rather than general anaesthetic.
- No incision is needed in the groin
- It avoids the bruising which can sometimes occur after standard surgery, but you may experience some lumpiness and tenderness in the thigh which can take several weeks to settle.
- Foam sclerotherapy or phlebectomies may be required to get rid of all the varicose veins. This may mean returning for treatment on another occasion.
- You can become fully active as quickly as you want after laser treatment.
- Most surgeons advise wearing a support stocking for 10 days and avoiding getting the legs wet (in a bath or shower).
- Laser treatment seems to give results as good as surgery up to five years but varicose veins may gradually reappear over the years.
- In summary, laser treatment can be done under local anaesthetic, requiring several injections into the thigh. Additional treatment may be needed to get rid of all the varicose veins.

Possible advantages and disadvantages of standard surgery.

- Standard surgery removes all the varicose veins at a single procedure. It should not be necessary to have anything more done to get rid of any remaining varicose veins.
- Varicose vein surgery is normally done under a general anaesthetic.
- Bruising is common. People with smaller varicose veins may get very little bruising but people with big varicose veins may be very bruised. All the bruising goes away.
- There may be some discomfort from the groin wound and occasionally the groin wound can become infected.
- You can become fully active as quickly as you want after standard surgery.
- Most surgeons advise wearing a support stocking for the first 10 days and avoiding getting the legs wet (in a bath or shower) during this time.
- Standard surgery gives a good long term result to many people but varicose veins may gradually reappear over the years.
- It is a tried and tested treatment which has been used for many years.
- In summary, surgical treatment involves a general anaesthetic, an incision in the groin and often some bruising. However, all the varicose veins can be dealt with thoroughly by a single treatment, in one or both legs.

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

Inclusion criteria

- Adult patients (aged over 18 years old) referred for treatment of primary varicose veins
- Symptomatic (CEAP grade 2 or above) primary long or short saphenous main stem incompetence (reflux >1 second on duplex scanning)
- Suitable for laser, foam sclerotherapy or surgery

Clinic date

.....

Study Number	Patient Name	Does the patient fulfill the inclusion/ exclusion criteria?	Is the patient potentially interested in taking part?	*If not eligible or declines to participate, state reason (A, B, C, D or E)*	If eligible and interested, record contact telephone number	Rx rec'd (F/S/ L)
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			
		Yes ☐ No ☐	Yes ☐ No ☐			

Exclusion criteria

A0: No varicose veins
A1: Thread veins
A2: Non-symptomatic (CEAP 1/2)
A3: No truncal reflux, or truncal reflux <1second
A4: Long or short saphenous less than 3mm or greater than 15mm in diameter
A5: Recurrence
A6: Tortuous veins that are considered unsuitable for EVLA
A7: Thrombosis (Current deep vein or acute superficial vein thrombosis)

B: Patient co-morbidity
- Cardiac failure
- Pulmonary oedema
- Local or systemic infection
- Pregnancy or breast feeding
- History of hypercoagulability
- Inability to mobilise post-procedure
- Varicosities caused by pelvic or abdominal tumours
- Arterial disease (ankle brachial pressure index <0.8)
- Patients who are not fit for a general anaesthetic due to significant systemic disease, morbid obesity or other causes.
- Migraines which are frequent, or migraines which are severe enough to require hospitalisation

C: Other
- Allergy to sclerosant
- Needle phobia
- Inability to complete questionnaires

D: Non attendance (DNA/CNA)
E1: Refusal - preference surgery
E2: Refusal - preference foam
E3: Refusal - preference laser
E4: Refusal - reason other than preference

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

Study Number

TRIAL CONSENT FORM

Please initial ALL boxes

By signing this form and initialling each box I agree that I have:

- read and understood the patient information leaflet (Version number ……., dated ……..) for the above study and kept a copy ☐
- discussed this study with Dr/Mr/Mrs/Ms …… and all my questions have received satisfactory answers ☐
- understood the purpose of the study and I know what my involvement will be ☐

I understand that:

- my participation is voluntary ☐
- if further funding is obtained I will be followed up for five years ☐
- I am free to withdraw from the study at any time without having to give a reason ☐
- if I withdraw, this will not affect my care ☐
- my personal data will be collected and stored at the Trial office in Aberdeen ☐
- information relevant to the CLASS trial may be collected from my hospital and NHS records, including Office of National Statistics (ONS) and NHS central registers ☐
- relevant sections of my medical notes and data collected during the study may be looked at by individuals directly involved in the trial, from regulatory authorities, from the University of Aberdeen or from the NHS Boards or Trusts, where it is relevant to my taki ng part in this research. ☐

I agree that my family doctor (GP), my hospital consultant and the person I have nominated as my best contact may be told that I am taking part in this study ☐

I agree to take part in the study ☐

Your signature (participant) _____

Your name in block capitals _____

Date _____

For office use only I confirm that I have explained to the person named above, the nature and purpose of the study and the procedures involved.

Signature _____

Date _____

CLASS Trial Office, Health Services Research Unit, University of Aberdeen, Scotland AB25 2ZD

Phone 01224 XXXXXX; Fax 01224 XXXXXX; xxxxxxxxx@abdn.ac.uk

Copies: 1 for patient; 1 for study notes, 1 for researcher in Aberdeen; 1 to be filed with hospital notes.

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

CONTACT DETAILS

Study number | | | | | | |

PATIENT DETAILS

Title ☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other

First name

Surname

Date of birth D D / M M / Y Y Y Y

Address

Home telephone

Mobile telephone

Work telephone

GP DETAILS

Initials Surname

Address

BEST CONTACT DETAILS

Title ☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other

First name

Surname

Address

Telephone number

RELATIONSHIP OF BEST CONTACT TO PATIENT

☐ Relative Please specify ☐ Friend

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

BASELINE CLINICAL DATA

Study Number | | | | | | |

AFFECTED LEG(S)

Right leg only ☐ Left leg only ☐ Both legs ☐

STUDY LEG (in case of bilaterality, study leg designated as worst leg by patient)

Right leg ☐ Left leg ☐

LEFT LEG: CEAP CLASSIFICATION

Please tick appropriate response

- ☐ C0 No visible or palpable signs of venous disease.
- ☐ C1 Telangiectasis or reticular veins. Veins less than 3 mm
- ☐ C2 Varicose veins. Veins over 3 mm
- ☐ C3 Edema
- ☐ C4 Skin and subcutaneous changes
- ☐ C4a Pigmentation or eczema
- ☐ C4b Lipodermatosclerosis or atrophie blanche
- ☐ C5 Healed venous ulcer
- ☐ C6 Active venous ulcer

LEFT LEG: Venous Clinical Severity Score (VCSS)

Left leg affected by varicose veins ☐ Yes ☐ No

If yes, complete VCSS by ticking **one box in each row**

PAIN

☐ None	☐ Occasional, not restricting activity or requiring analgesics	☐ Daily, moderate activity limitation, occasional analgesics	☐ Daily, severe limiting activities or requiring regular use of analgesics

VARICOSE VEINS i.e. >3mm

☐ None	☐ Few, scattered branch varicose veins	☐ Multiple: LSV varicose veins confined to calf or thigh	☐ Extensive: thigh and calf or LSV and SSV distribution

VENOUS EDEMA

☐ None	☐ Evening ankle only	☐ Afternoon edema, above ankle	☐ Morning edema above ankle and requiring activity change, elevation

SKIN PIGMENTATION

☐ None or focal, low intensity (tan)	☐ Diffuse, but limited in area and old (brown)	☐ Diffuse over most of gaiter area (lower 1/3) or recent pigmentation (purple)	☐ Wider distribution (above lower 1/3), recent pigmentation

INFLAMMATION

☐ None	☐ Mild cellulitis, limited to marginal area around ulcer	☐ Moderate cellulitis, involves most of gaiter area (lower 2/3)	☐ Severe cellulitis (lower 1/3 and above) or significant venous eczema

INDURATION

☐ None	☐ Focal, circum-malleolar (<5 cm)	☐ Medial or lateral, less than lower 1/3 of leg	☐ Entire lower 1/3 of leg or more

ACTIVE ULCERS, N

☐ 0	☐ 1	☐ 2	☐ >2

ACTIVE ULCERATION DURATION (longest duration; if 3 months, select >3 months

☐ None	☐ <3 months	☐ >3 months, <1year	☐ Not healed >1 year

ACTIVE ULCER, SIZE (largest ulcer)

☐ None	☐ <2 cm diameter	☐ 2-6 cm diameter	☐ >6 cm diameter

COMPRESSIVE THERAPY

☐ Not used or not compliant	☐ Intermittent use of stockings	☐ Wears elastic stockings most days	☐ Full compliance: stockings + elevation

RIGHT LEG: CEAP Classification

Please tick appropriate response

- ☐ C0 No visible or palpable signs of venous disease.
- ☐ C1 Telangiectasis or reticular veins. Veins less than 3 mm
- ☐ C2 Varicose veins. Veins over 3 mm
- ☐ C3 Edema
- ☐ C4 Skin and subcutaneous changes
- ☐ C4a Pigmentation or eczema
- ☐ C4b Lipodermatosclerosis or atrophie blanche
- ☐ C5 Healed venous ulcer
- ☐ C6 Active venous ulcer

RIGHT LEG: Venous Clinical Severity Score (VCSS)

Right leg affected by varicose veins ☐ Yes ☐ No

If yes, complete VCSS by ticking **one box in each row**

PAIN

☐ None	☐ Occasional, not restricting activity or requiring analgesics	☐ Daily, moderate activity limitation, occasional analgesics	☐ Daily, severe limiting activities or requiring regular use of analgesics

VARICOSE VEINS i.e. >3mm

☐ None	☐ Few, scattered branch varicose veins	☐ Multiple: LSV varicose veins confined to calf or thigh	☐ Extensive: thigh and calf or LSV and SSV distribution

VENOUS EDEMA

☐ None	☐ Evening ankle only	☐ Afternoon edema, above ankle	☐ Morning edema above ankle and requiring activity change, elevation

SKIN PIGMENTATION

☐ None or focal, low intensity (tan)	☐ Diffuse, but limited in area and old (brown)	☐ Diffuse over most of gaiter area (lower 1/3) or recent pigmentation (purple)	☐ Wider distribution (above lower 1/3), recent pigmentation

INFLAMMATION

☐ None	☐ Mild cellulitis, limited to marginal area around ulcer	☐ Moderate cellulitis, involves most of gaiter area (lower 2/3)	☐ Severe cellulitis (lower 1/3 and above) or significant venous eczema

INDURATION

☐ None	☐ Focal, circum-malleolar (<5 cm)	☐ Medial or lateral, less than lower 1/3 of leg	☐ Entire lower 1/3 of leg or more

ACTIVE ULCERS, N

☐ 0	☐ 1	☐ 2	☐ >2

ACTIVE ULCERATION DURATION (longest duration; if 3 months, select >3 months

☐ None	☐ <3 months	☐ >3 months, <1year	☐ Not healed >1 year

ACTIVE ULCER, SIZE (largest ulcer)

☐ None	☐ <2 cm diameter	☐ 2-6 cm diameter	☐ >6 cm diameter

COMPRESSIVE THERAPY

☐ Not used or not compliant	☐ Intermittent use of stockings	☐ Wears elastic stockings most days	☐ Full compliance: stockings + elevation

BRIEF CLINICAL HISTORY

	Yes	No
Previous history of DVT	☐	☐

If yes, give details

	Yes	No
Previous treatment of varicose veins to contra-lateral leg	☐	☐

If yes, type of treatment:

- Laser treatment ☐
- Surgery ☐
- Foam sclerotherapy ☐

	Yes	No
Previous foam sclerotherapy or sclerotherapy to tributaries of study leg	☐	☐

Duplex scan of study leg

Reflux >1s at the following sites	Yes	No	Not examined
Groin - long saphenous origin	☐	☐	☐
Deep vein just below SF junction (common femoral / superficial vein)	☐	☐	☐
Mid thigh - long saphenous	☐	☐	☐
Above knee - long saphenous	☐	☐	☐
Below knee - long saphenous	☐	☐	☐
Popliteal fossa - short saphenous origin	☐	☐	☐
Popliteal vein (below SP junction)	☐	☐	☐
Mid calf - short saphenous	☐	☐	☐

Diameter of trunk vein

		Not measured
Widest diameter below sapheno-femoral junction	mm	☐
Widest diameter below sapheno-popliteal junction	mm	☐

Summary of vein involvement on study leg

Long saphenous ☐ Yes ☐ No

Short saphenous ☐ Yes ☐ No

Date of scan D D / M M / Y Y Y Y

Name of person performing duplex scan

Comments on scan, including tortuousity, depth

CRITERIA FOR STUDY ENTRY

(all criteria must be fulfilled)

Study leg:

- Must have primary varicose veins ☐
- CEAP grade 2 or above ☐
- Size of vein: greater than 3mm and less than 15mm ☐
- 1 second reflux present ☐
- Must be suitable for laser treatment - vein depth ☐
- Must be suitable for laser treatment - tortuousity ☐

RANDOMISATION

Date of randomisation D D / M M / Y Y Y Y

TREATMENT ALLOCATION

Surgery	Foam sclerotherapy	Laser therapy
☐	☐	☐

Name of person undertaking randomisation

HEIGHT & WEIGHT

Height (in cm) ☐☐☐ Weight (in kg) ☐☐☐

EMPLOYMENT STATUS

Self-employed ☐ An employee ☐ Other ☐ → Please specify below

_____

PHYSICAL ACTIVITY

Type and amount of physical activity involved in your work (mark one box only)

I am not in employment (e.g. retired, retired for health reasons, unemployed, full-time carer etc) ☐

I spend most of my time at work sitting (such as in an office) ☐

I spend most of my time at work standing or walking. However, my work does not require much intense physical effort (e.g. shop assistant, hairdresser, security guard, childminder etc.) ☐

My work involves definite physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, cleaner, hospital nurse, gardener, postal delivery workers etc) ☐

My work involves vigorous physical activity including handling of very heavy objects (e.g. scaffolder, construction worker, refuse collector, etc.) ☐

During the last week, how many hours did you spend on each of the following activities? (mark one box on each row)

	None	Some but less than 1 hour	1 hour but less than 3 hours	3 hours or more
Physical exercise such as swimming, jogging, aerobics, football, tennis, gym workout etc.	☐	☐	☐	☐
Cycling, including cycling to work and during leisure time	☐	☐	☐	☐
Walking, including walking to work, shopping, for pleasure etc.	☐	☐	☐	☐
Housework/childcare	☐	☐	☐	☐
Gardening/DIY	☐	☐	☐	☐

How would you describe your usual walking pace? (mark one box only)

Slow pace (i.e. less than 3 mph) ☐ Steady average pace ☐ Brisk pace ☐ Fast pace (i.e. over 4 mph) ☐

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

PRESENCE OF VARICOSE VEINS

Study Number | | | | | | |

STUDY LEG

Right leg ☐ Left leg ☐

We would like to know how you see the amount of varicose veins on your leg.
On the scale below, please indicate how many varicose veins you think you have.

No varicose veins — The most varicose veins I can imagine

For office use only:

Completed by: Participant ☐ Research nurse ☐

Timepoint: Baseline ☐ Six weeks ☐ Six months ☐

NB: the participant and research nurse should complete this independently.

RECRUITMENT QUESTIONNAIRE

Study Number

CLASS

Comparison of **LA**ser, **S**urgery and foam **S**clerotherapy

Confidential

Thank you for helping us with our research.
We would be very grateful if you could complete this questionnaire.

ISRCTN51995477
EudraCT 2008-001069-26

Version 3
February 2009

SECTION A: DESCRIBING YOUR OWN HEALTH TODAY – (EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

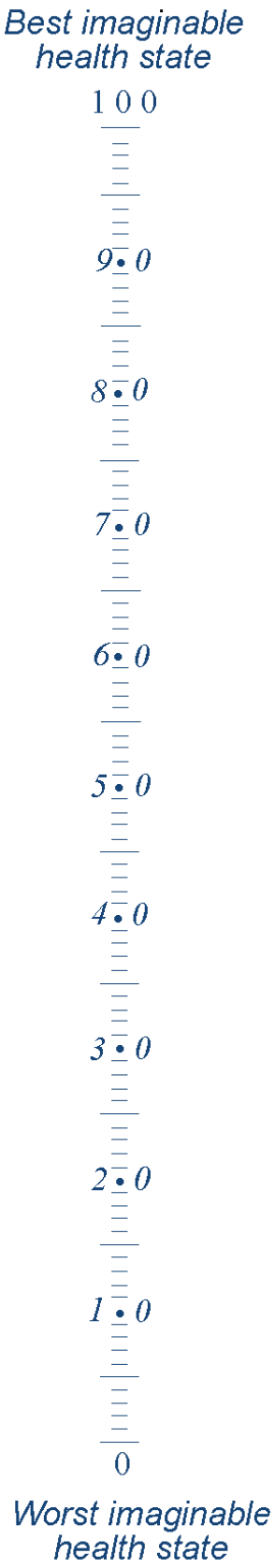
A1.	**Mobility**	I have no problems in walking about	☐
		I have some problems in walking about	☐
		I am confined to bed	☐
A2.	**Self-care**	I have no problems with self-care	☐
		I have some problems washing or dressing myself	☐
		I am unable to wash or dress myself	☐
A3.	**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
		I have some problems with performing my usual activities	☐
		I am unable to perform my usual activities	☐
A4.	**Pain/Discomfort**	I have no pain or discomfort	☐
		I have moderate pain or discomfort	☐
		I have extreme pain or discomfort	☐
A5.	**Anxiety/Depression**	I am not anxious or depressed	☐
		I am moderately anxious or depressed	☐
		I am extremely anxious or depressed	☐

A6. Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today

Your health state today



SECTION B: YOUR GENERAL HEALTH (SF-36)

Please fill in all the questions by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

B1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

B2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

B3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sport	☐	☐	☐
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c) Lifting or carrying groceries	☐	☐	☐
d) Climbing **several** flights of stairs	☐	☐	☐
e) Climbing **one** flight of stairs	☐	☐	☐
f) Bending, kneeling or stooping	☐	☐	☐
g) Walking **more than one mile**	☐	☐	☐
h) Walking **several hundred yards**	☐	☐	☐
i) Walking **one hundred yards**	☐	☐	☐
j) Bathing and dressing yourself	☐	☐	☐

B4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example it took extra effort)	☐	☐	☐	☐	☐

B5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

B6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

B7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

B8. **During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

B9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

B10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

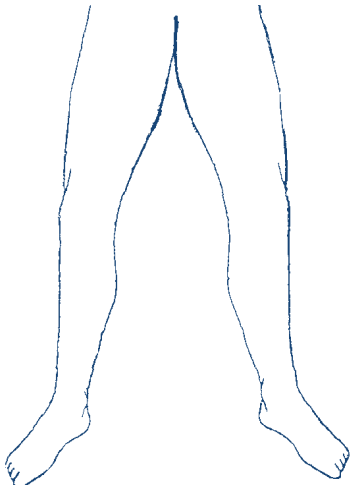
B11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anyone I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

SECTION C: YOUR VARICOSE VEINS

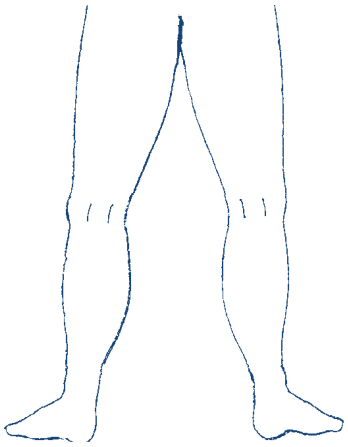
C1. Please draw in your varicose veins in the diagram(s) below:-

Legs viewed from the front



Right Left

Legs viewed from the back



Left Right

C2. In the last two weeks, for how many days did your varicose veins cause you pain or ache? ***(Please cross one box for each leg)***

	Right Leg	Left Leg
None at all	☐	☐
Between 1 and 5 days	☐	☐
Between 6 and 10 days	☐	☐
For more than 10 days	☐	☐

C3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins? (*Please cross one box)*

None at all	☐
Between 1 and 5 days	☐
Between 6 and 10 days	☐
For more than 10 days	☐

C4. In the last two weeks, how much ankle swelling have you had? (*Please cross one box*)

None at all	☐
Slight ankle swelling	☐
Moderate ankle swelling (causing you to sit with your feet up whenever possible)	☐
Severe ankle swelling (causing you difficulty putting on your shoes)	☐

C5. In the last two weeks, have you worn support stockings or tights? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, those I bought myself without a doctor's prescription	☐	☐
Yes, those my doctor prescribed for me which I wear occasionally	☐	☐
Yes, those my doctor prescribed for me which I wear every day	☐	☐

C6. In the last two weeks, have you had any itching in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Both above and below the knee	☐	☐

C7. Do you have any purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C8. Do you have a rash or eczema in the area of your ankle? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, but it does not require any treatment from a doctor or district nurse	☐	☐
Yes, and it requires treatment from my doctor or district nurse	☐	☐

C9. Do you have a skin ulcer associated with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C10. Does the appearance of your varicose veins cause you concern? (*Please cross one box*)

No	☐
Yes, their appearance causes me slight concern	☐
Yes, their appearance causes me moderate concern	☐
Yes, their appearance causes me a great deal of concern	☐

C11. Does the appearance of your varicose veins influence your choice of clothing including tights? (*Please cross one box*)

- No ☐
- Occasionally ☐
- Often ☐
- Always ☐

C12. During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities? (*Please cross one box*)

- No ☐
- I have been able to work but my work has suffered to a slight extent ☐
- I have been able to work but my work has suffered to a moderate extent ☐
- My veins have prevented me from working one day or more ☐

C13. During the last two weeks have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)? (*Please cross one box*)

- No ☐
- Yes, my enjoyment has suffered to a slight extent ☐
- Yes, my enjoyment has suffered to a moderate extent ☐
- Yes, my veins have prevented me taking part in any leisure activities ☐

SECTION D: YOUR SYMPTOMS

Listed below are a number of symptoms that you may or may not have experienced since you developed varicose veins.

Please indicate by crossing *Yes* or *No* whether you have experienced any of these symptoms since you developed varicose veins, and whether you believe that these symptoms are related to your varicose veins.

		I have experienced this symptom *since I developed varicose veins*		This symptom is *related to my varicose veins*	
D1.	Pain	Yes ☐	No ☐	Yes ☐	No ☐
D2.	Hardening of the skin on the legs	Yes ☐	No ☐	Yes ☐	No ☐
D3.	Redness of the skin on the legs	Yes ☐	No ☐	Yes ☐	No ☐
D4.	Sleep difficulties	Yes ☐	No ☐	Yes ☐	No ☐
D5.	Swelling of the ankle	Yes ☐	No ☐	Yes ☐	No ☐
D6.	Discolouration or brown staining on the leg	Yes ☐	No ☐	Yes ☐	No ☐
D7.	Stiff joints	Yes ☐	No ☐	Yes ☐	No ☐
D8.	Weight loss	Yes ☐	No ☐	Yes ☐	No ☐
D9.	Dizziness	Yes ☐	No ☐	Yes ☐	No ☐
D10.	Fatigue	Yes ☐	No ☐	Yes ☐	No ☐
D11.	Breaks in the skin or ulcers on the leg	Yes ☐	No ☐	Yes ☐	No ☐
D12.	Sore eyes	Yes ☐	No ☐	Yes ☐	No ☐
D13.	Breathlessness	Yes ☐	No ☐	Yes ☐	No ☐
D14.	Loss of strength	Yes ☐	No ☐	Yes ☐	No ☐

SECTION E: YOUR VIEWS ABOUT YOUR VARICOSE VEINS

We are interested in your own personal views of how you now see your varicose veins. Please indicate how much you agree or disagree with the following statements about your varicose veins by crossing the appropriate box.

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
E1. My varicose veins will last a short time	☐	☐	☐	☐	☐
E2. My varicose veins are likely to be permanent rather than temporary	☐	☐	☐	☐	☐
E3. My varicose veins will last for a long time	☐	☐	☐	☐	☐
E4. These varicose veins will pass quickly	☐	☐	☐	☐	☐
E5. I expect to have these varicose veins for the rest of my life	☐	☐	☐	☐	☐
E6. My varicose veins are a serious condition	☐	☐	☐	☐	☐
E7. My varicose veins have major consequences on my life	☐	☐	☐	☐	☐
E8. My varicose veins do not have much effect on my life	☐	☐	☐	☐	☐
E9. My varicose veins strongly affect the way others see me	☐	☐	☐	☐	☐
E10. My varicose veins have serious financial consequences	☐	☐	☐	☐	☐
E11. My varicose veins cause difficulties for those who are close to me	☐	☐	☐	☐	☐
E12. There is a lot which I can do to control my symptoms	☐	☐	☐	☐	☐

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
E13. What I do can determine whether my varicose veins get better or worse	☐	☐	☐	☐	☐
E14. The course of my varicose veins depends on me	☐	☐	☐	☐	☐
E15. Nothing I do will affect my varicose veins	☐	☐	☐	☐	☐
E16. I have the power to influence my varicose veins	☐	☐	☐	☐	☐
E17. My actions will have no effect on the outcome of my varicose veins	☐	☐	☐	☐	☐
E18. My varicose veins will improve in time	☐	☐	☐	☐	☐
E19. There is very little that can be done to improve my varicose veins	☐	☐	☐	☐	☐
E20. My treatment will be effective in curing my varicose veins	☐	☐	☐	☐	☐
E21. The negative effects of my varicose veins can be prevented (avoided) by my treatment	☐	☐	☐	☐	☐
E22. My treatment can control my varicose veins	☐	☐	☐	☐	☐
E23. There is nothing which can help my varicose veins	☐	☐	☐	☐	☐
E24. The symptoms of my varicose veins are puzzling to me	☐	☐	☐	☐	☐
E25. My varicose veins are a mystery to me	☐	☐	☐	☐	☐

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
E26. I don't understand my varicose veins	☐	☐	☐	☐	☐
E27. My varicose veins don't make any sense to me	☐	☐	☐	☐	☐
E28. I have a clear picture or understanding of my varicose veins	☐	☐	☐	☐	☐
E29. The symptoms of my varicose veins change a great deal from day to day	☐	☐	☐	☐	☐
E30. My symptoms come and go in cycles	☐	☐	☐	☐	☐
E31. My varicose veins are very unpredictable	☐	☐	☐	☐	☐
E32. I go through cycles in which my varicose veins get better and worse	☐	☐	☐	☐	☐
E33. I get depressed when I think about my varicose veins	☐	☐	☐	☐	☐
E34. When I think about my varicose veins I get upset	☐	☐	☐	☐	☐
E35. My varicose veins make me feel angry	☐	☐	☐	☐	☐
E36. My varicose veins do not worry me	☐	☐	☐	☐	☐
E37. Having these varicose veins makes me feel anxious	☐	☐	☐	☐	☐
E38. My varicose veins make me feel afraid	☐	☐	☐	☐	☐

SECTION F: CAUSES OF YOUR VARICOSE VEINS

We are interested in what you consider may have been the cause of your varicose veins. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your varicose veins rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your varicose veins. Please indicate how much you agree or disagree that they were causes for you by crossing the appropriate box.

Possible causes	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
F1. Stress or worry	☐	☐	☐	☐	☐
F2. Hereditary - it runs in my family	☐	☐	☐	☐	☐
F3. A germ or virus	☐	☐	☐	☐	☐
F4. Diet or eating habits	☐	☐	☐	☐	☐
F5. Chance or bad luck	☐	☐	☐	☐	☐
F6. Poor medical care in my past	☐	☐	☐	☐	☐
F7. Pollution in the environment	☐	☐	☐	☐	☐
F8. My own behaviour	☐	☐	☐	☐	☐
F9. My mental attitude, e.g. thinking about life negatively	☐	☐	☐	☐	☐
F10. Family problems or worries caused my varicose veins	☐	☐	☐	☐	☐
F11. Overwork	☐	☐	☐	☐	☐
F12. My emotional state, e.g. feeling down, lonely, anxious, empty	☐	☐	☐	☐	☐
F13. Ageing	☐	☐	☐	☐	☐
F14. Alcohol	☐	☐	☐	☐	☐
F15. Smoking	☐	☐	☐	☐	☐
F16. Accident or injury	☐	☐	☐	☐	☐
F17. My personality	☐	☐	☐	☐	☐
F18. Altered immunity	☐	☐	☐	☐	☐

In the table below, please list in rank-order the three most important factors that you now believe caused your varicose veins. You may use any of the items from the previous page, or you may have additional ideas of your own.

The most important causes for me:-

1. _____

2. _____

3. _____

THANK YOU

Thank you very much for your time and patience in filling in this questionnaire. Please hand the questionnaire back to the research nurse or return it in the enclosed reply-paid envelope to the Trial Office in Aberdeen.

The information you have given us will be extremely useful in helping us carry out research. It will be treated with the strictest confidence and kept securely.

Thank you again for your help

If you would like any further information or have any queries about the study, please contact:

The CLASS Trial Office in Aberdeen (Tel: 01224 XXXXXX)

This study is taking place across the UK but the questionnaires are being processed in Aberdeen at The Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, Health Sciences Building, Foresterhill, ABERDEEN, AB25 2ZD.

Reminder letter to participants who do not return baseline questionnaire

Date

<<Title>> <<Name>> << Surname>> *Study No.*
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>«Address3»
<<Postcode>>«Address4»

Dear <<Title>> <<Surname>>

Title of Study:

Thank you very much for taking part in the XXX Study.

When you attended your appointment with the research nurse recently, we gave you a questionnaire to take home and complete. Unfortunately we have not yet received it back from you (if it is in the post, sorry to bother you and please ignore this reminder).

We are keen to find out how you are before your varicose veins are treated. It is very important for the success of the study that we have as much information as possible about you.

Some of the questions may not seem relevant but we would be very grateful if you could try to fill them all in. If you have any problems in completing the questionnaires, a friend or relative may be able to help you. Alternatively, please contact the CLASS Study Office; we will be happy to help in any way we can.

Please return the questionnaire in the reply-paid envelope provided.

In the meantime, if you require any further help or information about the Study, please contact the Study office.

Yours sincerely

Letter to participant confirming what treatment they have been randomised to

Date

<<Title>> <<Name>> << Surname>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>«Address3»
<<Postcode>>«Address4»

Study No.

Dear <<Title>> <<Surname>>

Title of Study:

Thank you very much for taking part in the CLASS Study.

You should have received an appointment for the treatment of your varicose veins. This will have been sent direct from the hospital. If you have not received an appointment, please do get in touch with the CLASS study office. The treatment you have been allocated is xxx. You can read more about the treatment in the leaflet on varicose veins and treatment that you received from the CLASS study. If you would like another copy of this leaflet, please get in touch with us and we can send one to you.

We enclose a questionnaire as we are keen to find out whether your views on your varicose veins have changed since you agreed to take part in the study.

Some of the questions may not seem relevant but we would be very grateful if you could try to fill them all in. If you have any problems in completing the questionnaires, a friend or relative may be able to help you. Alternatively, please contact the CLASS Study Office; we will be happy to help in any way we can.

Please return the questionnaire in the reply-paid envelope provided.

If you have any questions, or require any further information about the Study, please contact the Study office.

Yours sincerely

Letter to GP informing them of their patient's participation in CLASS

Date

Dr <<GP Name>> << GP Surname>>
<<GP Address 1>>
<<GP Address 2>>
<<GP Address 3>>
<<GP Address 4>>«Address3»
<<GP Postcode>>«Address4»

Dear Dr <<Surname>>

Patient Details <<title >> <<Name>> << Surname>>

Date of birth: <<dob>>

Address: <<patient address>>

Title of Study: **RANDOMISED CONTROLLED TRIAL COMPARING FOAM SCLEROTHERAPY, ALONE OR IN COMBINATION WITH ENDOVENOUS LASER THERAPY, WITH CONVENTIONAL SURGERY AS TREATMENT FOR VARICOSE VEINS**

Vascular Surgeons: [*insert names of local surgeons*]

Your patient has agreed to take part in this study. This is a major research study funded by the Health Technology Assessment (HTA) programme of the NHS, taking place in [*insert site*] and in five other sites throughout the UK. It is comparing three different kinds of treatments for varicose veins - conventional surgery, foam sclerotherapy and endovenous laser therapy in terms of their clinical and cost-effectiveness.

Patients receive written information regarding the study and the various treatment options at their initial out-patient clinic visit and are then contacted to ask if they wish to take part. If they agree they attend to provide consent and to have a full baseline assessment. They are then randomised to one of the treatments. Following treatment, patients will be followed up at 6 weeks and 6 months at a clinic appointment for clinical examination, a duplex scan and completion of a questionnaire.

I hope that you would be in accord with your patient participating in this study. The aim is to provide robust data to guide the treatment of varicose veins. Your patient will have been given clear written information about the potential benefits and disadvantages of the trial and we will only involve them after fully informed consent. Please do not hesitate to contact me if you have any concerns about your patient being included in this study.

With best wishes,

Yours sincerely

Letter to GP informing them of the treatment to which the patient has been randomised

Date

Dr <<GP Name>> << GP Surname>>
<<GP Address 1>>
<<GP Address 2>>
<<GP Address 3>>
<<GP Address 4>>«Address3»
<<GP Postcode>>«Address4»

Dear Dr <<Surname>>

Patient Details <<title >> <<Name>> << Surname>>

Date of birth: <<dob>>

Address: <<patient address>>

Title of Study: **RANDOMISED CONTROLLED TRIAL COMPARING FOAM SCLEROTHERAPY, ALONE OR IN COMBINATION WITH ENDOVENOUS LASER THERAPY, WITH CONVENTIONAL SURGERY AS TREATMENT FOR VARICOSE VEINS**

Vascular surgeons: [*insert names of local surgeons*]

As you know from our previous letter, your patient has agreed to take part in this study. This is a major research study funded by the Health Technology Assessment (HTA) programme of the NHS, taking place in six sites throughout the UK. It is comparing three different kinds of treatments for varicose veins - conventional surgery, foam sclerotherapy and endovenous laser therapy in terms of their clinical and cost-effectiveness.

Your patient has been randomised to receive <<treatment allocation>>, and, if they have not already received an appointment for this, they will receive one shortly.

Please do not hesitate to contact me if you have any concerns about your patient being included in this study.

With best wishes,

Yours sincerely

PRE-TREATMENT QUESTIONNAIRE

Study Number

CLASS

Comparison of **LA**ser, **S**urgery and foam **S**clerotherapy

Confidential

Thank you for helping us with our research.
We would be very grateful if you could complete this questionnaire.

ISRCTN51995477
EudraCT 2008-001069-26

Version 2
August 2008

SECTION A: YOUR SYMPTOMS

Listed below are a number of symptoms that you may or may not have experienced since you developed varicose veins.

Please indicate by ticking *Yes* or *No* whether you have experienced any of these symptoms since you developed varicose veins, and whether you believe that these symptoms are related to your varicose veins.

		I have experienced this symptom *since I developed varicose veins*		This symptom is *related to my varicose veins*	
A1.	Pain	Yes ☐	No ☐	Yes ☐	No ☐
A2.	Hardening of the skin on the legs	Yes ☐	No ☐	Yes ☐	No ☐
A3.	Redness of the skin on the legs	Yes ☐	No ☐	Yes ☐	No ☐
A4.	Sleep difficulties	Yes ☐	No ☐	Yes ☐	No ☐
A5.	Swelling of the ankle	Yes ☐	No ☐	Yes ☐	No ☐
A6.	Discolouration or brown staining on the leg	Yes ☐	No ☐	Yes ☐	No ☐
A7.	Stiff joints	Yes ☐	No ☐	Yes ☐	No ☐
A8.	Weight loss	Yes ☐	No ☐	Yes ☐	No ☐
A9.	Dizziness	Yes ☐	No ☐	Yes ☐	No ☐
A10.	Fatigue	Yes ☐	No ☐	Yes ☐	No ☐
A11.	Breaks in the skin or ulcers on the leg	Yes ☐	No ☐	Yes ☐	No ☐
A12.	Sore eyes	Yes ☐	No ☐	Yes ☐	No ☐
A13.	Breathlessness	Yes ☐	No ☐	Yes ☐	No ☐
A14.	Loss of strength	Yes ☐	No ☐	Yes ☐	No ☐

SECTION B: YOUR VIEWS ABOUT YOUR VARICOSE VEINS

We are interested in your own personal views of how you now see your varicose veins. Please indicate how much you agree or disagree with the following statements about your varicose veins by ticking the appropriate box.

Views about your varicose veins		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
B1.	My varicose veins will last a short time	☐	☐	☐	☐	☐
B2.	My varicose veins are likely to be permanent rather than temporary	☐	☐	☐	☐	☐
B3.	My varicose veins will last for a long time	☐	☐	☐	☐	☐
B4.	These varicose veins will pass quickly	☐	☐	☐	☐	☐
B5.	I expect to have these varicose veins for the rest of my life	☐	☐	☐	☐	☐
B6.	My varicose veins are a serious condition	☐	☐	☐	☐	☐
B7.	My varicose veins have major consequences on my life	☐	☐	☐	☐	☐
B8.	My varicose veins do not have much effect on my life	☐	☐	☐	☐	☐
B9.	My varicose veins strongly affect the way others see me	☐	☐	☐	☐	☐
B10.	My varicose veins have serious financial consequences	☐	☐	☐	☐	☐
B11.	My varicose veins cause difficulties for those who are close to me	☐	☐	☐	☐	☐
B12.	There is a lot which I can do to control my symptoms	☐	☐	☐	☐	☐

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
B13. What I do can determine whether my varicose veins get better or worse	☐	☐	☐	☐	☐
B14. The course of my varicose veins depends on me	☐	☐	☐	☐	☐
B15. Nothing I do will affect my varicose veins	☐	☐	☐	☐	☐
B16. I have the power to influence my varicose veins	☐	☐	☐	☐	☐
B17. My actions will have no effect on the outcome of my varicose veins	☐	☐	☐	☐	☐
B18. My varicose veins will improve in time	☐	☐	☐	☐	☐
B19. There is very little that can be done to improve my varicose veins	☐	☐	☐	☐	☐
B20. My treatment will be effective in curing my varicose veins	☐	☐	☐	☐	☐
B21. The negative effects of my varicose veins can be prevented (avoided) by my treatment	☐	☐	☐	☐	☐
B22. My treatment can control my varicose veins	☐	☐	☐	☐	☐
B23. There is nothing which can help my varicose veins	☐	☐	☐	☐	☐
B24. The symptoms of my varicose veins are puzzling to me	☐	☐	☐	☐	☐
B25. My varicose veins are a mystery to me	☐	☐	☐	☐	☐

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
B26. I don't understand my varicose veins	☐	☐	☐	☐	☐
B27. My varicose veins don't make any sense to me	☐	☐	☐	☐	☐
B28. I have a clear picture or understanding of my varicose veins	☐	☐	☐	☐	☐
B29. The symptoms of my varicose veins change a great deal from day to day	☐	☐	☐	☐	☐
B30. My symptoms come and go in cycles	☐	☐	☐	☐	☐
B31. My varicose veins are very unpredictable	☐	☐	☐	☐	☐
B32. I go through cycles in which my varicose veins get better and worse	☐	☐	☐	☐	☐
B33. I get depressed when I think about my varicose veins	☐	☐	☐	☐	☐
B34. When I think about my varicose veins I get upset	☐	☐	☐	☐	☐
B35. My varicose veins make me feel angry	☐	☐	☐	☐	☐
B36. My varicose veins do not worry me	☐	☐	☐	☐	☐
B37. Having these varicose veins makes me feel anxious	☐	☐	☐	☐	☐
B38. My varicose veins make me feel afraid	☐	☐	☐	☐	☐

SECTION C: CAUSES OF YOUR VARICOSE VEINS

We are interested in what you consider may have been the cause of your varicose veins. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your varicose veins rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your varicose veins. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

Possible causes	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
C1. Stress or worry	☐	☐	☐	☐	☐
C2. Hereditary - it runs in my family	☐	☐	☐	☐	☐
C3. A germ or virus	☐	☐	☐	☐	☐
C4. Diet or eating habits	☐	☐	☐	☐	☐
C5. Chance or bad luck	☐	☐	☐	☐	☐
C6. Poor medical care in my past	☐	☐	☐	☐	☐
C7. Pollution in the environment	☐	☐	☐	☐	☐
C8. My own behaviour	☐	☐	☐	☐	☐
C9. My mental attitude, e.g. thinking about life negatively	☐	☐	☐	☐	☐
C10. Family problems or worries caused my varicose veins	☐	☐	☐	☐	☐
C11. Overwork	☐	☐	☐	☐	☐
C12. My emotional state, e.g. feeling down, lonely, anxious, empty	☐	☐	☐	☐	☐
C13. Ageing	☐	☐	☐	☐	☐
C14. Alcohol	☐	☐	☐	☐	☐
C15. Smoking	☐	☐	☐	☐	☐
C16. Accident or injury	☐	☐	☐	☐	☐
C17. My personality	☐	☐	☐	☐	☐
C18. Altered immunity	☐	☐	☐	☐	☐

In the table below, please list in rank-order the three most important factors that you now believe caused your varicose veins. You may use any of the items from the previous page, or you may have additional ideas of your own.

The most important causes for me:-

1. _____

2. _____

3. _____

THANK YOU

Thank you very much for your time and patience in filling in this questionnaire. Please hand the questionnaire back to the research nurse or return it in the enclosed reply-paid envelope to the Trial Office in Aberdeen.

The information you have given us will be extremely useful in helping us carry out research. It will be treated with the strictest confidence and kept securely.

Thank you again for your help

If you would like any further information or have any queries about the study, please contact:

The CLASS Trial Office in Aberdeen (Tel: 01224 XXXXXX)

This study is taking place across the UK but the questionnaires are being processed in Aberdeen at The Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, Health Sciences Building, Foresterhill, ABERDEEN, AB25 2ZD.

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

SURGERY

Study Number | | | | | | |

Study leg Right ☐ Left ☐

(defined at baseline; in bilateral cases study leg designated as worst affected leg **by patient**)

Date of surgery D D / M M / Y Y Y Y

Confirmation that patient is eligible for treatment:

A: Vein - exclusion criteria Eligible ☐ Not eligible ☐

- CEAP 0/1, non-symptomatic
- Reflux <1 second
- Current deep vein thrombosis
- Acute superficial vein thrombosis
- Long or short saphenous vein less than 3mm in diameter or greater than 15mm
- Tortuous veins that are considered to be unsuitable for EVLA due to difficulties in passing the guide wire

B: Patient co-morbidity - exclusion criteria Eligible ☐ Not eligible ☐

- Cardiac failure
- Pulmonary oedema
- Local or systemic infection
- Pregnancy or breast feeding
- History of hypercoagulability
- Inability to mobilise post-procedure
- Varicosities caused by pelvic or abdominal tumours
- Arterial disease (ankle brachial pressure index <0.8)
- Patients who are not fit for a general anaesthetic due to significant systemic disease, morbid obesity or other causes.

If patient is not eligible for treatment they should not be treated in CLASS

Was the participant randomised to receive SURGERY? Yes ☐ No ☐

If No, please give reason why the participant is receiving SURGERY

Details of treatment to study leg

Long saphenous vein		Yes ☐		No ☐
If yes:				
	Stripping to	Above knee ☐		Below knee ☐
	Phlebectomies	Yes ☐		No ☐

Short saphenous vein		Yes ☐		No ☐
If yes:				
	Stripping to	Below knee ☐		
	Phlebectomies	Yes ☐		No ☐

Grade of surgeon

Consultant	☐			
Staff grade	☐	Supervised by consultant	Yes ☐	No ☐
Trainee	☐	Supervised by consultant	Yes ☐	No ☐

Grade of anaesthetist present

Consultant	☐	Associate specialist	☐
Staff grade	☐	Registrar	☐
SHO	☐		

Type of anaesthesia

General	☐		Epidural/spinal		☐
SC HEPARIN or derivative	Yes	☐	No		☐
HRT	Yes	☐		No	☐
Oral contraceptive	Yes	☐		No	☐

Timings

Please use 24 hour clock

	H H : m m
Time of entry into anaesthetic room	

Operating time
(time between starting preparation of the patient and finishing bandaging)

	H H : m m
Time of starting preparation of patient	
Time of finishing bandaging	
Time of leaving operating room	
Time of leaving recovery room	

Was planned treatment completed?

Yes ☐ No ☐

If No, give reason

Contra-lateral leg

Was contra-lateral leg treated at same time? Yes ☐ No ☐

Stocking/bandage to study leg			
Length	Full ☐	Knee ☐	
Make / grade			
Recommended duration according to protocol (10 days)	Yes ☐	No ☐	
If No: recommended duration	Days		
Reason for duration of bandaging not 10 days			

Procedural complications (before discharge)			
Procedural complications	Yes ☐	No ☐	
If yes, give details below:			
Wound haematoma *If Yes:*	Yes ☐	No ☐	
Required drainage	Yes ☐	No ☐	
Required overnight stay	Yes ☐	No ☐	
Bleeding *If Yes:*	Yes ☐	No ☐	
Required overnight stay	Yes ☐	No ☐	
Damage to major artery*	Yes ☐	No ☐	
If yes:	Common femoral ☐	Superficial femoral ☐	Popliteal ☐
Damage to major vein*	Yes ☐	No ☐	
If yes:	Common femoral ☐	Popliteal ☐	
Damage to major nerve*	Yes ☐	No ☐	
If yes:	Femoral ☐	Tibial ☐	Peroneal ☐
Other	Yes ☐	No ☐	
If yes, give details			

*** Details of these should also be reported as a Serious Adverse Event.**

Anaesthetic side effects

Anaesthetic side effects	Yes ☐	No ☐
If yes, give details below:		
Blurred vision	Yes ☐	No ☐
Sickness	Yes ☐	No ☐
Muscle pains	Yes ☐	No ☐
Headache	Yes ☐	No ☐
Sore throat	Yes ☐	No ☐
Damage to teeth, lip or tongue	Yes ☐	No ☐
Allergic/anaphylactiod reactions	Yes ☐	No ☐
Other	Yes ☐	No ☐
If yes, give details		

Time in hospital

Planned day-case	Yes ☐	No ☐
Planned overnight stay	Yes ☐	No ☐
Unexpected overnight stay	Yes ☐	No ☐

Reason for admission

Date admitted to hospital D D / M M / Y Y Y Y

Date discharged from hospital D D / M M / Y Y Y Y

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

FOAM SCLEROTHERAPY

Study Number | | | | | | |

Study leg Right ☐ Left ☐

(defined at baseline; in bilateral cases study leg designated as worst affected leg **by patient**)

Date of foam sclerotherapy D D / M M / Y Y Y Y

Confirmation that patient is eligible for treatment:

A: Vein - exclusion criteria Eligible ☐ Not eligible ☐

- CEAP 0/1, non-symptomatic
- Reflux <1 second
- Current deep vein thrombosis
- Acute superficial vein thrombosis
- Long or short saphenous vein less than 3mm in diameter or greater than 15mm
- Tortuous veins that are considered to be unsuitable for EVLA due to difficulties in passing the guide wire

B: Patient co-morbidity - exclusion criteria Eligible ☐ Not eligible ☐

- Cardiac failure
- Pulmonary oedema
- Local or systemic infection
- Pregnancy or breast feeding
- History of hypercoagulability
- Inability to mobilise post-procedure
- Varicosities caused by pelvic or abdominal tumours
- Arterial disease (ankle brachial pressure index <0.8)
- Patients who are not fit for a general anaesthetic due to significant systemic disease, morbid obesity or other causes.

C: Other Eligible ☐ Not eligible ☐

- Allergy to sclerosant.

If patient is not eligible for treatment they should not be treated in CLASS

Is the patient receiving foam sclerotherapy in accordance with their randomisation (i.e. they were randomised to FOAM SCLEROTHERAPY, or were randomised to EVLA and are receiving foam following EVLA)? Yes ☐ No ☐

If No, please give reason why the participant is receiving FOAM SCLEROTHERAPY?

Details of treatment to study leg

Long saphenous vein Yes ☐ No ☐

If yes, Confirm Fibrovein ☐ Fibrovein:air ratio 1:3 ☐ 3% ☐

Manufacturer's lot/batch number

Expiry date D D / M M / Y Y Y Y

Total volume of foam ml

Short saphenous vein Yes ☐ No ☐

If yes, Confirm Fibrovein ☐ Fibrovein:air ratio 1:3 ☐ 3% ☐

Manufacturer's lot/batch number As above ☐

Expiry date D D / M M / Y Y Y Y As above ☐

Total volume of foam ml

Non-truncal varicosites Yes - calf ☐ Yes - thigh ☐ No ☐

If yes, Confirm Fibrovein ☐ Fibrovein:air ratio 1:3 ☐ 1% ☐

Manufacturer's lot/batch number

Expiry date D D / M M / Y Y Y Y

Total volume of foam ml

Local anaesthetic

Yes ☐ No ☐

If yes: Type of anaesthetic

Concentration

Volume

SC HEPARIN or derivative Yes ☐ No ☐

HRT Yes ☐ No ☐

Oral contraceptive Yes ☐ No ☐

Grade of surgeon performing treatment

Consultant ☐

Staff grade ☐ Supervised by consultant Yes ☐ No ☐

Trainee ☐ Supervised by consultant Yes ☐ No ☐

Consultant nurse ☐ Supervised by consultant Yes ☐ No ☐

Duration

Please use 24 hour clock H H m m

Time of entry into treatment room ☐☐ : ☐☐

Treatment time

Time of start (preparation of patient) ☐☐ : ☐☐

Time of finish (completion of bandaging) ☐☐ : ☐☐

Time of leaving treatment room ☐☐ : ☐☐

Was planned treatment completed? Yes ☐ No ☐

If No, give reason

Stocking/bandage to study leg

Confirm that bandaging according to protocol - Velband/PehaHaft/Credelast stockings, for ten days — Yes ☐ No ☐

If not according to protocol:

Type of bandaging applied

Recommended duration ____ Days

Reason why bandaging not according to protocol

Contra-lateral leg

Was contra-lateral leg treated at same time? Yes ☐ No ☐

Procedural complications (noted at time of treatment)

Procedural complications Yes ☐ No ☐

If yes, give details below:

Visual disturbance Yes ☐ No ☐

If yes, give details

Headache Yes ☐ No ☐

If yes, migraine with aura ☐ headache ☐

Transient confusion Yes ☐ No ☐

If yes, give details/duration

Panic attack Yes ☐ No ☐

If yes, give details/duration

Malaise Yes ☐ No ☐

If yes, give details/duration

Cough Yes ☐ No ☐

If yes, give details/duration

Chest tightness/heaviness Yes ☐ No ☐

If yes, give details/duration		
Vasovagal	Yes ☐	No ☐
If yes, give details/duration		
Extravasation of foam	Yes ☐	No ☐
If yes, give details		
Anaphylacoid reaction*	Yes ☐	No ☐
If yes, give details		
Stroke*	Yes ☐	No ☐
If yes, state hemisphere and Rankin grade		
Transient ischaemic attack†	Yes ☐	No ☐
If yes, give details		
Myocardial infarction*	Yes ☐	No ☐
If yes, give details		
Intra-arterial injection*	Yes ☐	No ☐
If yes, give details		
Epileptic fit*	Yes ☐	No ☐
If yes, give details/duration		
Other	Yes ☐	No ☐
If yes, give details		

*** Details of these should also be reported as a Serious Adverse Event.**
Permanent loss of vision should also be reported as a Serious Adverse Event.
† If hospitalised after transient ischaemic attack or other complication, this should also be reported as a serious adverse event.

Hospital admission

Was the patient admitted to hospital immediately after the procedure?

Yes ☐ No ☐

If yes:

Reason for admission ☐

Date of admission D D / M M / Y Y Y Y

Date of discharge D D / M M / Y Y Y Y

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

LASER THERAPY

Study Number | | | | | | |

Study leg Right ☐ Left ☐

(defined at baseline; in bilateral cases study leg designated as worst affected leg **by patient**)

Date of laser therapy D D / M M / Y Y Y Y

Confirmation that patient is eligible for treatment:

A: Vein - exclusion criteria Eligible ☐ Not eligible ☐

- CEAP 0/1, non-symptomatic
- Reflux <1 second
- Current deep vein thrombosis
- Acute superficial vein thrombosis
- Long or short saphenous vein less than 3mm in diameter or greater than 15mm
- Tortuous veins that are considered to be unsuitable for EVLA due to difficulties in passing the guide wire

B: Patient co-morbidity - exclusion criteria Eligible ☐ Not eligible ☐

- Cardiac failure
- Pulmonary oedema
- Local or systemic infection
- Pregnancy or breast feeding
- History of hypercoagulability
- Inability to mobilise post-procedure
- Varicosities caused by pelvic or abdominal tumours
- Arterial disease (ankle brachial pressure index <0.8)
- Patients who are not fit for a general anaesthetic due to significant systemic disease, morbid obesity or other causes.

If patient is not eligible for treatment they should not be treated in CLASS

Was the participant randomised to receive LASER THERAPY? Yes ☐ No ☐

If No, please give reason why the participant is receiving LASER THERAPY

Details of treatment to study leg

Long saphenous vein Yes ☐ No ☐

If Yes:

Cannulation Above knee ☐ Below knee ☐

Laser delivery Continuous ☐ Interrupted ☐

Watts _____ Joules _____

Length (cm) _____ Joules/cm _____

Laser type/wavelength _____

Plebectomies Yes ☐ No ☐ N/A (Centres other than Hull) ☐

Short saphenous vein Yes ☐ No ☐

If Yes:

Cannulation Above knee ☐ Below knee ☐

Laser delivery Continuous ☐ Interrupted ☐

Watts _____ Joules _____

Length (cm) _____ Joules/cm _____

Laser type/wavelength _____

Plebectomies Yes ☐ No ☐ N/A (Centres other than Hull) ☐

Local anaesthetic to study leg

Skin Yes ☐ No ☐

If yes: Type

Concentration

Tumescent Yes ☐ No ☐

If yes: Cooled Yes ☐ No ☐

Volume of tumescent ml

Anaesthetic added to Tumescent Yes ☐ No ☐

Type of anaesthetic

Concentration

Sedation Yes ☐ No ☐

If yes: Give details

SC HEPARIN or derivative Yes ☐ No ☐

HRT Yes ☐ No ☐

Oral contraceptive Yes ☐ No ☐

Grade of surgeon performing laser therapy

Consultant ☐

Staff grade ☐ Supervised by consultant Yes ☐ No ☐

Trainee ☐ Supervised by consultant Yes ☐ No ☐

Duration

Please use 24 hour clock

Time of entry into treatment room — H H : m m

Treatment time

Time of start (preparation of patient) — H H : m m

Time of finish (completion of bandaging) — H H : m m

Time of leaving treatment room — H H : m m

Was planned treatment completed? Yes ☐ No ☐

If No, give reason

Stocking/bandage

Length — Full ☐ Knee ☐

Make / grade

Recommended duration according to protocol (10 days) — Yes ☐ No ☐

If No: recommended duration ____ days

Reason for duration of bandaging not 10 days

Contra-lateral leg

Was contra-lateral leg treated at same time? — Yes ☐ No ☐

Procedural complications (noted at time of treatment)

Procedural complications	Yes ☐	No ☐
If yes, give details below:		
Wound haematoma	Yes ☐	No ☐
If yes:		
Required drainage	Yes ☐	No ☐
Required overnight stay	Yes ☐	No ☐
Damage to major vein*	Yes ☐	No ☐
If yes:	Femoral ☐	Popliteal ☐
Other	Yes ☐	No ☐
If yes, give details		

***Details of these should also be reported as a serious adverse event**

Hospital admission

Was the patient admitted to hospital immediately after the procedure?

Yes ☐ No ☐

If yes:

Reason for admission

Date of admission D D / M M / Y Y Y Y

Date of discharge D D / M M / Y Y Y Y

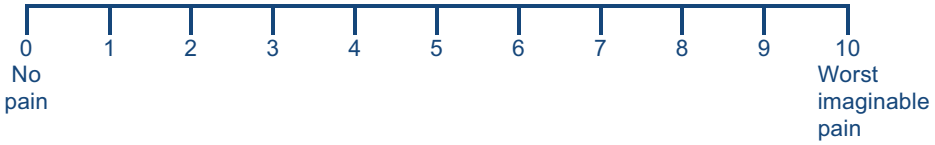
CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

PAIN DURING TREATMENT

Study Number | | | | | | |

Please rate the worst pain that you experienced while you were having your treatment. The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a cross (X) on the line that best indicates the rating of the pain you experienced while you were having your treatment for varicose veins.



CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

6 WEEK ASSESSMENT

Study Number | | | | | | |

STUDY LEG

Right ☐ Left ☐

Date of 6 week assessment

D D / M M / Y Y Y Y

DUPLEX SCAN Complete for **study leg only**

	Not examined	Complete occlusion (absent)	Partial occlusion	No occlusion (patent)	If patent, is reflux: Present	If patent, is reflux: Absent
Groin - long saphenous (flush with CFV - ie within 1cm)	☐	☐	☐	☐	☐	☐
Groin - long saphenous (within 3cm of CFV)	☐	☐	☐	☐	☐	☐
Common femoral/superficial vein*	☐	☐	☐	☐	☐	☐
Mid thigh - long saphenous	☐	☐	☐	☐	☐	☐
Above knee - long saphenous	☐	☐	☐	☐	☐	☐
Below knee - long saphenous	☐	☐	☐	☐	☐	☐
Short saphenous (flush with popliteal - i.e. within 1cm)	☐	☐	☐	☐	☐	☐
Short saphenous (within 3cm of popliteal)	☐	☐	☐	☐	☐	☐
Popliteal vein*	☐	☐	☐	☐	☐	☐
Mid calf - short saphenous	☐	☐	☐	☐	☐	☐

* Occlusion in the common femoral vein or popliteal fossa-popliteal vein (DVT) should be reported as a Serious Adverse Event (if not already reported)

Name of person performing duplex scan

Date of duplex scan D D / M M / Y Y Y Y

CEAP CLASSIFICATION

Complete for **study leg only** - Please tick appropriate response

☐	C0	No visible or palpable signs of venous disease.
☐	C1	Telangiectasis or reticular veins. Veins less than 3 mm
☐	C2	Varicose veins. Veins over 3 mm
☐	C3	Edema
☐	C4	Skin and subcutaneous changes
☐	C4a	Pigmentation or eczema
☐	C4b	Lipodermatosclerosis or atrophie blanche
☐	C5	Healed venous ulcer
☐	C6	Active venous ulcer

VENOUS CLINICAL SEVERITY SCORE (VCSS)

Complete for study leg only

PAIN

☐ None	☐ Occasional, not restricting activity or requiring analgesics	☐ Daily, moderate activity limitation, occasional analgesics	☐ Daily, severe limiting activities or requiring regular use of analgesics

VARICOSE VEINS i.e. >3mm

☐ None	☐ Few, scattered branch varicose veins	☐ Multiple: GSV varicose veins confined to calf or thigh	☐ Extensive: thigh and calf or GSV and SSV distribution

VENOUS EDEMA

☐ None	☐ Evening ankle only	☐ Afternoon edema, above ankle	☐ Morning edema above ankle and requiring activity change, elevation

SKIN PIGMENTATION

☐ None or focal, low intensity (tan)	☐ Diffuse, but limited in area and old (brown)	☐ Diffuse over most of gaiter area (lower 1/3) or recent pigmentation (purple)	☐ Wider distribution (above lower 1/3), recent pigmentation

INFLAMMATION

☐ None	☐ Mild cellulitis, limited to marginal area around ulcer	☐ Moderate cellulitis, involves most of gaiter area (lower 2/3)	☐ Severe cellulitis (lower 1/3 and above) or significant venous eczema

INDURATION

☐ None	☐ Focal, circum-malleolar (<5 cm)	☐ Medial or lateral, less than lower 1/3 of leg	☐ Entire lower 1/3 of leg or more

ACTIVE ULCERS, N

☐ 0	☐ 1	☐ 2	☐ >2

ACTIVE ULCERATION DURATION

☐ None	☐ <3 months	☐ >3 months, <1year	☐ Not healed >1 year

ACTIVE ULCER, SIZE

☐ None	☐ <2 cm diameter	☐ 2-6 cm diameter	☐ >6 cm diameter

COMPRESSIVE THERAPY

☐ Not used or not compliant	☐ Intermittent use of stockings	☐ Wears elastic stockings most days	☐ Full compliance: stockings + elevation

COMPLICATIONS

Numbness Yes ☐ No ☐

If yes: state distribution/dimensions

Persistent bruising Yes ☐ No ☐

If yes: state distribution/dimensions

Persistent tenderness/discomfort Yes ☐ No ☐

If yes: state distribution/dimensions

Skin loss/ulceration Yes ☐ No ☐

If yes: state distribution/dimensions

Lumpiness Yes ☐ No ☐

If yes: state distribution/dimensions

Development of thread vein Yes ☐ No ☐

If yes: state distribution/dimensions

Skin staining Yes ☐ No ☐

If yes: state distribution/dimensions

Wound infection Yes ☐ No ☐

If yes:

Required antibiotics Yes ☐ No ☐

Required drainage Yes ☐ No ☐

Required hospital admission Yes ☐ No ☐

Back-ache Yes ☐ No ☐

If yes: give details

Headache Yes ☐ No ☐

If yes: give details

Deep vein thrombosis* Yes ☐ No ☐

If yes: state distribution/dimensions					
Pulmonary embolus*	Yes ☐		No ☐		
If yes: give details of severity					
Stroke*	Yes ☐		No ☐		
If yes: state hemisphere and Rankin grade					
Myocardial infarction*	Yes ☐		No ☐		
If yes: give details					
Loss of vision*	Yes ☐		No ☐		
If yes: give details					
Damage to major artery*	Yes ☐		No ☐		
If yes:	Common femoral ☐		Superficial femoral ☐		
Damage to major vein*	Yes ☐		No ☐		
If yes:	Common femoral ☐		Popliteal ☐		
Damage to motor nerve*	Yes ☐		No ☐		
If yes:	Femoral ☐		Tibial ☐	Popliteal ☐	
Other	Yes ☐		No ☐		
If yes: give details					

***If not previously reported as a Serious Adverse Event, details of these should be reported as a Serious Adverse Event.**

HOSPITAL ADMISSIONS

	Yes	No
Has the participant been admitted to hospital for any reason since the initial procedure?	☐	☐

If yes: give reason

Hospital admitted to

Date admitted D D / M M / Y Y Y Y

Date discharged D D / M M / Y Y Y Y

TREATMENT TO STUDY LEG OUTWITH THE CLASS TRIAL PROTOCOL

	Yes	No
Has the participant had treatment to the study leg outwith the CLASS trial protocol since being recruited to CLASS?	☐	☐

If yes, give date of treatment D D / M M / Y Y Y Y

details of treatment

TREATMENT TO CONTRALATERAL LEG

	Yes	No
Has the participant had treatment to the contralateral leg since being recruited to CLASS?	☐	☐

If yes, give date of treatment D D / M M / Y Y Y Y

details of treatment

SIX WEEK QUESTIONNAIRE

Study Number

CLASS

Comparison of **LA**ser, **S**urgery and foam **S**clerotherapy

Confidential

Thank you for helping us with our research.
We would be very grateful if you could complete this questionnaire.

ISRCTN51995477
EudraCT 2008-001069-26

Version 4
February 2009

SECTION A: DESCRIBING YOUR OWN HEALTH TODAY – (EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today.

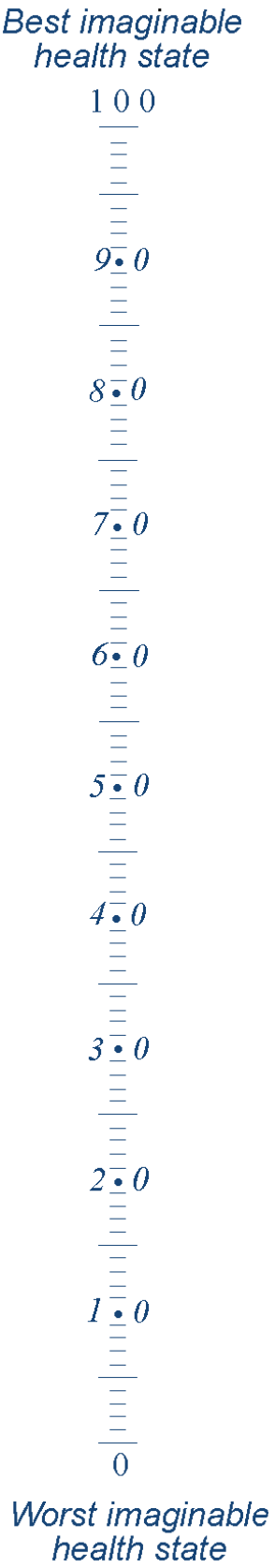
A1.	**Mobility**	I have no problems in walking about	☐
		I have some problems in walking about	☐
		I am confined to bed	☐
A2.	**Self-care**	I have no problems with self-care	☐
		I have some problems washing or dressing myself	☐
		I am unable to wash or dress myself	☐
A3.	**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
		I have some problems with performing my usual activities	☐
		I am unable to perform my usual activities	☐
A4.	**Pain/Discomfort**	I have no pain or discomfort	☐
		I have moderate pain or discomfort	☐
		I have extreme pain or discomfort	☐
A5.	**Anxiety/Depression**	I am not anxious or depressed	☐
		I am moderately anxious or depressed	☐
		I am extremely anxious or depressed	☐

A6. Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today.

Your health state today



SECTION B: YOUR GENERAL HEALTH (SF-36)

Please fill in all the questions by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

B1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

B2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

B3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sport	☐	☐	☐
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c) Lifting or carrying groceries	☐	☐	☐
d) Climbing **several** flights of stairs	☐	☐	☐
e) Climbing **one** flight of stairs	☐	☐	☐
f) Bending, kneeling or stooping	☐	☐	☐
g) Walking **more than one mile**	☐	☐	☐
h) Walking **several hundred yards**	☐	☐	☐
i) Walking **one hundred yards**	☐	☐	☐
j) Bathing and dressing yourself	☐	☐	☐

B4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example it took extra effort)	☐	☐	☐	☐	☐

B5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

B6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

B7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

B8. **During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

B9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

B10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?**

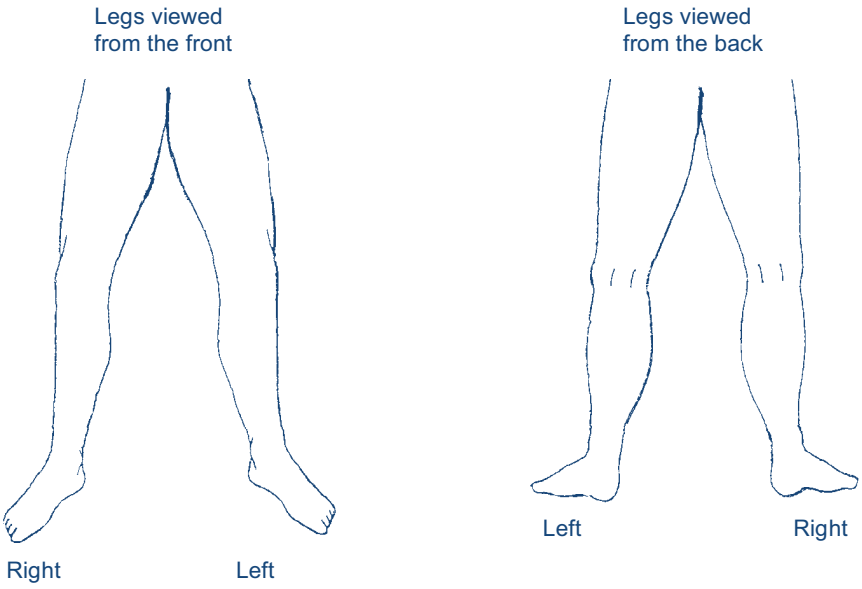
All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

B11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anyone I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

SECTION C: YOUR VARICOSE VEINS

C1. Please draw in your varicose veins in the diagram(s) below:



C2. In the last two weeks, for how many days did your varicose veins cause you pain or ache? ***(Please cross one box for each leg)***

	Right Leg	Left Leg
None at all	☐	☐
Between 1 and 5 days	☐	☐
Between 6 and 10 days	☐	☐
For more than 10 days	☐	☐

C3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins? (*Please cross one box)*

None at all	☐
Between 1 and 5 days	☐
Between 6 and 10 days	☐
For more than 10 days	☐

C4. In the last two weeks, how much ankle swelling have you had? (*Please cross one box*)

None at all	☐
Slight ankle swelling	☐
Moderate ankle swelling (causing you to sit with your feet up whenever possible)	☐
Severe ankle swelling (causing you difficulty putting on your shoes)	☐

C5. In the last two weeks, have you worn support stockings or tights? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, those I bought myself without a doctor's prescription	☐	☐
Yes, those my doctor prescribed for me which I wear occasionally	☐	☐
Yes, those my doctor prescribed for me which I wear every day	☐	☐

C6. In the last two weeks, have you had any itching in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Both above and below the knee	☐	☐

C7. Do you have any purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C8. Do you have a rash or eczema in the area of your ankle? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, but it does not require any treatment from a doctor or district nurse	☐	☐
Yes, and it requires treatment from my doctor or district nurse	☐	☐

C9. Do you have a skin ulcer associated with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C10. Does the appearance of your varicose veins cause you concern? (*Please cross one box*)

No	☐
Yes, their appearance causes me slight concern	☐
Yes, their appearance causes me moderate concern	☐
Yes, their appearance causes me a great deal of concern	☐

C11. Does the appearance of your varicose veins influence your choice of clothing including tights? (*Please cross one box*)

No	☐
Occasionally	☐
Often	☐
Always	☐

C12. During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities? (Please cross one box)

- No ☐
- I have been able to work but my work has suffered to a slight extent ☐
- I have been able to work but my work has suffered to a moderate extent ☐
- My veins have prevented me from working one day or more ☐

C13. During the last two weeks have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)? (*Please cross one box*)

- No ☐
- Yes, my enjoyment has suffered to a slight extent ☐
- Yes, my enjoyment has suffered to a moderate extent ☐
- Yes, my veins have prevented me taking part in any leisure activities ☐

SECTION D: YOUR RECOVERY

In this section we are interested in your activities during your recovery from your treatment for varicose veins. This includes questions on:

- **for how long you wore your support stocking(s)**
- **how soon after your treatment you were able to do certain activities without discomfort**
- **whether you did anything yourself to try and help your recovery.**

It may be hard for you to remember the answers to some of these questions, but it would be really helpful if you could be as accurate as you can be from your memory.

First of all, we are interested in *how long* you wore your support stocking(s).

EXAMPLE OF HOW TO COMPLETE THIS QUESTION
If you wore your stocking(s) all the time (day and night, i.e. 24 hours) for 5 days, then, during the day only for a further 3 weeks, you would complete the question as follows:

I wore my support stocking(s):

☐ Not at all

☒ Day and night (i.e. 24 hours) for [5] days, then during the day only for [21] days

☐ Other (please explain) [ ]

EXAMPLE

PLEASE NOW COMPLETE THIS BOX TO TELL US HOW LONG YOU WORE YOUR SUPPORT STOCKING(S)

PLEASE CROSS THE RELEVANT BOX AND COMPLETE THE SENTENCE

I wore my support stocking(s):

☐ Not at all

☐ Day and night (i.e. 24 hours) for [ ] days, then during the day only for [ ] days

☐ Other (please explain) [ ]

For each of the following activities we are interested in:

- **whether you do not normally do this activity; or**
- **whether you normally do this activity but have not yet done so since your treatment; or**
- ***how soon after your treatment* for varicose veins you carried out this activity.**

EXAMPLES OF HOW TO COMPLETE THESE QUESTIONS

If you first had a bath or shower 6 days after treatment, you would answer as follows:

Having a bath or shower:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☒ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☒ 6 days after my treatment OR ☐ weeks after my treatment

EXAMPLE

If you never drive a car, you would cross the box as follows:

Driving a car:

☒ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

EXAMPLE

THE FOLLOWING QUESTIONS ARE FOR YOU TO ANSWER

1. Bending the leg(s) (without discomfort):

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

2. Lifting heavy objects (without discomfort):

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

3. Moving from a standing to a sitting position (without discomfort):

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

4. Standing still for a long time i.e. more than 15 minutes (without discomfort):

- ☐ I don't normally do this
- ☐ I normally do this, but haven't done so since my treatment
- ☐ I have done this since my treatment. I did it for the first time:
  - ☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

5. Walking short distances i.e. less than 20 minutes (without discomfort):

- ☐ I don't normally do this
- ☐ I normally do this, but haven't done so since my treatment
- ☐ I have done this since my treatment. I did it for the first time:
  - ☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

6. Walking long distances i.e. more than 20 minutes:

- ☐ I don't normally do this
- ☐ I normally do this, but haven't done so since my treatment
- ☐ I have done this since my treatment. I did it for the first time:
  - ☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

7. Having a bath or shower:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

8. Driving a car:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

9. Doing housework:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

10. Looking after children:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

11. Wearing clothes that show the legs:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

12. Partial return to normal work/employment:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

13. Full return to normal work/employment:

☐ I don't normally do this

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

14. Going out socially (such as going to the cinema, theatre, a restaurant etc.):

Please describe a social activity that is important to you:

_____

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

15. Sporting activity or exercise (such as swimming, going to the gym, cycling, running, jogging, horse-riding, hill-walking, golf etc.):

Please describe a sporting activity that is important to you:

_____

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

16. Anything else that you do that is important to you, not already mentioned:

Please describe the activity:

_____

☐ I normally do this, but haven't done so since my treatment

☐ I have done this since my treatment. I did it for the first time:

☐ on the day of my treatment OR ☐ days after my treatment OR ☐ weeks after my treatment

Finally, was there anything that you did in order to help your recovery from your treatment for varicose veins? For example, keeping your leg raised while sitting.
Please complete the following sentence:

To help my recovery I _____

_____

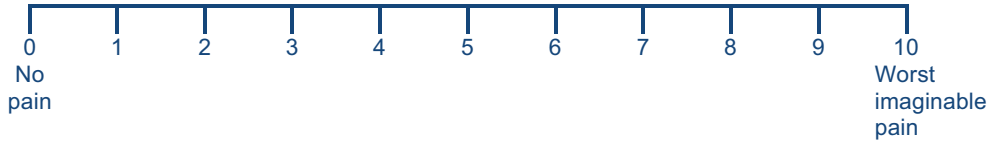
_____

_____

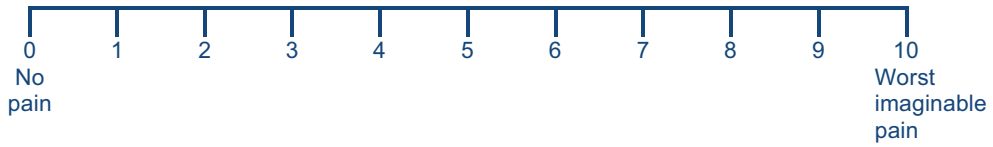
_____

SECTION E: PAIN

E1. **Please rate the worst pain that you experienced while you were having your treatment for varicose veins.** The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a cross (X) on the line that best indicates the rating of the pain you experienced while you were having your treatment for varicose veins.



E2. **Please rate the worst pain that you have experienced while recovering in the days and weeks after your treatment for varicose veins.** The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a cross (X) on the line that best indicates the rating of the pain you experienced while recovering from your treatment for varicose veins.



THANK YOU

Thank you very much for your time and patience in filling in this questionnaire. Please hand the questionnaire back to the research nurse or return it in the enclosed reply-paid envelope to the Trial Office in Aberdeen.

The information you have given us will be extremely useful in helping us carry out research. It will be treated with the strictest confidence and kept securely.

Thank you again for your help

If you would like any further information or have any queries about the study, please contact:

The CLASS Trial Office in Aberdeen (Tel: 01224 XXXXXX)

This study is taking place across the UK but the questionnaires are being processed in Aberdeen at The Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, Health Sciences Building, Foresterhill, ABERDEEN, AB25 2ZD.

Reminder letter to participants who do not return 6 week or 6 month questionnaire

Date

<<Title>> <<Name>> << Surname>> *Study No.*
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>«Address3»
<<Postcode>>«Address4»

Dear <<Title>> <<Surname>>

Title of Study:

Thank you very much for taking part in the CLASS Study.

When you attended your follow-up appointment recently, we gave you a questionnaire to take home and complete. Unfortunately we have not yet received it back from you (if it is in the post, sorry to bother you and please ignore this reminder).

We are keen to find out how you have been getting on since your varicose veins were treated. It is very important for the success of the study that we have as much information as possible about you.

Some of the questions may not seem relevant but we would be very grateful if you could try to fill them all in. If you have any problems in completing the questionnaires, a friend or relative may be able to help you. Alternatively, please contact the CLASS Study Office; we will be happy to help in any way we can.

Please return the questionnaire in the reply-paid envelope provided.

In the meantime, if you require any further help or information about the Study, please contact the Study office.

Yours sincerely

Cover letter to send with six-week questionnaire for patients who fail to attend for the six-week follow-up appointment

Date

<<Title>> <<Name>> << Surname>> *Study No.*
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>«Address3»
<<Postcode>>«Address4»

Dear <<Title>> <<Surname>>

Thank you very much for taking part in the CLASS Study.

We are sorry that you have been unable to attend a six-week follow-up appointment.

We are keen to find out how you have been getting on since your varicose veins were treated. It is very important for the success of the study that we have as much information as possible about you.

Some of the questions may not seem relevant but we would be very grateful if you could try to fill them all in. If you have any problems in completing the questionnaires, a friend or relative may be able to help you. Alternatively, please contact the CLASS Study Office; we will be happy to help in any way we can.

Please return the questionnaire in the reply-paid envelope provided.

In the meantime, if you require any further help or information about the Study, please contact the Study office. Likewise, if you would like to re-arrange a six-week follow-up appointment with the research nurse, please do contact …… on ……..

Yours sincerely

Reminder letter for the six-week or six month questionnaire for patients who fail to attend for the follow-up appointment

Date

<<Title>> <<Name>> << Surname>> *Study No.*
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>«Address3»
<<Postcode>>«Address4»

Dear <<Title>> <<Surname>>

Thank you very much for taking part in the CLASS Study.

Recently, we sent you a questionnaire to complete. Unfortunately we have not yet received it back from you (if it is in the post, sorry to bother you and please ignore this reminder).

We are keen to find out how you have been getting on since your varicose veins were treated. It is very important for the success of the study that we have as much information as possible about you.

Some of the questions may not seem relevant but we would be very grateful if you could try to fill them all in. If you have any problems in completing the questionnaires, a friend or relative may be able to help you. Alternatively, please contact the CLASS Study Office; we will be happy to help in any way we can.

Please return the questionnaire in the reply-paid envelope provided.

In the meantime, if you require any further help or information about the Study, please contact the Study office.

Yours sincerely

CLASS
Comparison of LAser, Surgery and foam Sclerotherapy

6 MONTH ASSESSMENT

Study Number | | | | | | |

STUDY LEG

Right ☐ Left ☐

Date of 6 month assessment

D D / M M / Y Y Y Y

DUPLEX SCAN Complete for study leg only

	Not examined	Complete occlusion (absent)	Partial occlusion	No occlusion (patent)	If patent, is reflux	
					Present	Absent
Groin - long saphenous (flush with CFV – i.e within 1cm)	☐	☐	☐	☐	☐	☐
Groin - long saphenous (within 3cm of CFV)	☐	☐	☐	☐	☐	☐
Common femoral/superficial vein*	☐	☐	☐	☐	☐	☐
Mid thigh - long saphenous	☐	☐	☐	☐	☐	☐
Above knee - long saphenous	☐	☐	☐	☐	☐	☐
Below knee - long saphenous	☐	☐	☐	☐	☐	☐
Short saphenous (flush with popliteal - i.e. within 1cm)	☐	☐	☐	☐	☐	☐
Short saphenous (within 3cm of popliteal)	☐	☐	☐	☐	☐	☐
Popliteal vein*	☐	☐	☐	☐	☐	☐
Mid calf - short saphenous	☐	☐	☐	☐	☐	☐

* Occlusion in the common femoral vein or popliteal fossa-popliteal vein (DVT) should be reported as a Serious Adverse Event (if not already reported)

Name of person performing duplex scan

Date of duplex scan D D / M M / Y Y Y Y

CEAP CLASSIFICATION Complete for study leg only - Please tick appropriate response		
☐	C0	No visible or palpable signs of venous disease.
☐	C1	Telangiectasis or reticular veins. Veins less than 3 mm
☐	C2	Varicose veins. Veins over 3 mm
☐	C3	Edema
☐	C4	Skin and subcutaneous changes
☐	C4a	Pigmentation or eczema
☐	C4b	Lipodermatosclerosis or atrophie blanche
☐	C5	Healed venous ulcer
☐	C6	Active venous ulcer

VENOUS CLINICAL SEVERITY SCORE (VCSS)
Complete for study leg only

PAIN

☐ None	☐ Occasional, not restricting activity or requiring analgesics	☐ Daily, moderate activity limitation, occasional analgesics	☐ Daily, severe limiting activities or requiring regular use of analgesics

VARICOSE VEINS i.e. >3mm

☐ None	☐ Few, scattered branch varicose veins	☐ Multiple: GSV varicose veins confined to calf or thigh	☐ Extensive: thigh and calf or GSV and SSV distribution

VENOUS EDEMA

☐ None	☐ Evening ankle only	☐ Afternoon edema, above ankle	☐ Morning edema above ankle and requiring activity change, elevation

SKIN PIGMENTATION

☐ None or focal, low intensity (tan)	☐ Diffuse, but limited in area and old (brown)	☐ Diffuse over most of gaiter area (lower 1/3) or recent pigmentation (purple)	☐ Wider distribution (above lower 1/3), recent pigmentation

INFLAMMATION

☐ None	☐ Mild cellulitis, limited to marginal area around ulcer	☐ Moderate cellulitis, involves most of gaiter area (lower 2/3)	☐ Severe cellulitis (lower 1/3 and above) or significant venous eczema

INDURATION

☐ None	☐ Focal, circum-malleolar (<5 cm)	☐ Medial or lateral, less than lower 1/3 of leg	☐ Entire lower 1/3 of leg or more

ACTIVE ULCERS, N

☐ 0	☐ 1	☐ 2	☐ >2

ACTIVE ULCERATION DURATION

☐ None	☐ <3 months	☐ >3 months, <1year	☐ Not healed >1 year

ACTIVE ULCER, SIZE

☐ None	☐ <2 cm diameter	☐ 2-6 cm diameter	☐ >6 cm diameter

COMPRESSIVE THERAPY

☐ Not used or not compliant	☐ Intermittent use of stockings	☐ Wears elastic stockings most days	☐ Full compliance: stockings + elevation

COMPLICATIONS		
Numbness	Yes ☐	No ☐
If yes: state distribution/dimensions		
Persistent tenderness/discomfort	Yes ☐	No ☐
If yes: state distribution/dimensions		
Skin loss/ulceration	Yes ☐	No ☐
If yes: state distribution/dimensions		
Lumpiness	Yes ☐	No ☐
If yes: state distribution/dimensions		
Development of thread vein	Yes ☐	No ☐
If yes: state distribution/dimensions		
Skin staining	Yes ☐	No ☐
If yes: state distribution/dimensions		
Deep vein thrombosis*	Yes ☐	No ☐
If yes: state distribution/dimensions		
Pulmonary embolus*	Yes ☐	No ☐
If yes: give details of severity		
Other	Yes ☐	No ☐
If yes, give details		

***If not already reported as a serious adverse event, details of these should be reported as a serious adverse event**

HOSPITAL ADMISSIONS

	Yes	No
Has the participant been admitted to hospital for any reason since the six week assessment?	☐	☐

If yes, give reason

Hospital admitted to

Date admitted D D / M M / Y Y Y Y

Date discharged D D / M M / Y Y Y Y

TREATMENT TO STUDY LEG OUTWITH THE CLASS TRIAL PROTOCOL

	Yes	No
Has the participant had treatment to the study leg outwith the CLASS trial protocol since being recruited to CLASS?	☐	☐

If yes, give date of treatment D D / M M / Y Y Y Y

details of treatment

TREATMENT TO CONTRALATERAL LEG

	Yes	No
Has the participant had treatment to the contralateral leg since being recruited to CLASS?	☐	☐

If yes, give date of treatment D D / M M / Y Y Y Y

details of treatment

DUPLEX SCANS TO STUDY LEG

	Yes	No
Apart from the scans undertaken at recruitment and at six week and six month follow-up, has the participant had any **additional scans** to the study leg since being recruited to CLASS?	☐	☐

If yes, give number of **additional** scans ☐

SIX MONTH QUESTIONNAIRE

Study Number

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

CONFIDENTIAL

Thank you for helping us with our research.
We would be very grateful if you could complete this questionnaire.

ISRCTN51995477
EudraCT 2008-001069-26

Version 4
April 2010

SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

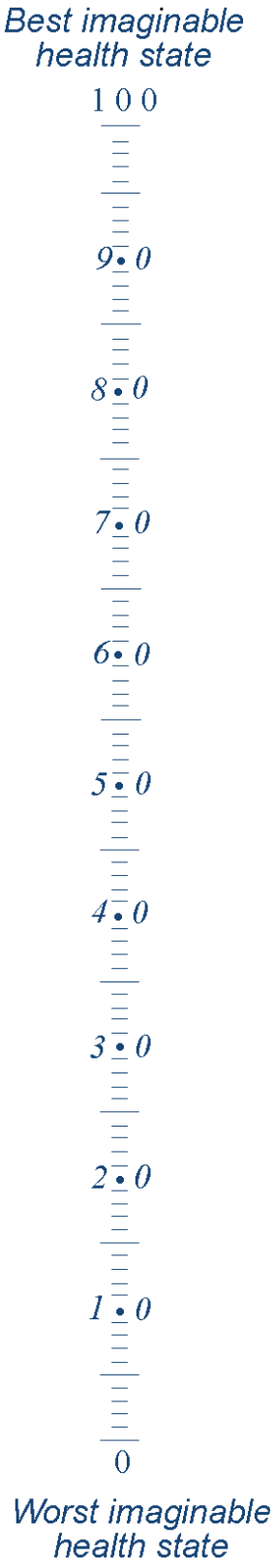
A1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
A3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

A6. **Please indicate on this scale how good or bad your own health state is today.**

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today.

Your health state today



SECTION B: YOUR GENERAL HEALTH (SF-36)

Please fill in all the questions by crossing the relevant box of the answer that applies to you. These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

B1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

B2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

B3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sport	☐	☐	☐
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c) Lifting or carrying groceries	☐	☐	☐
d) Climbing **several** flights of stairs	☐	☐	☐
e) Climbing **one** flight of stairs	☐	☐	☐
f) Bending, kneeling or stooping	☐	☐	☐
g) Walking **more than one mile**	☐	☐	☐
h) Walking **several hundred yards**	☐	☐	☐
i) Walking **one hundred yards**	☐	☐	☐
j) Bathing and dressing yourself	☐	☐	☐

B4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example it took extra effort)	☐	☐	☐	☐	☐

B5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

B6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

B7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

B8. **During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

B9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

B10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

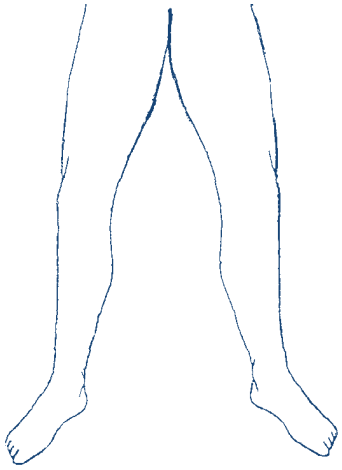
B11. **How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anyone I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

SECTION C: YOUR VARICOSE VEINS

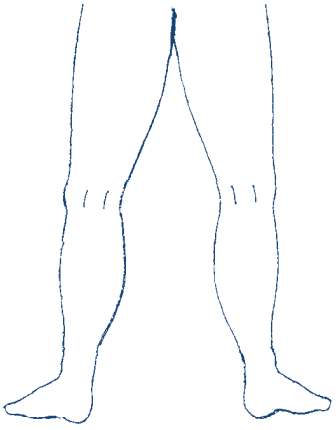
C1. **Please draw in your varicose veins in the diagram(s) below:-**

Legs viewed from the front



Right Left

Legs viewed from the back



Left Right

C2. In the last two weeks, for how many days did your varicose veins cause you pain or ache? ***(Please cross one box for each leg)***

	Right Leg	Left Leg
None at all	☐	☐
Between 1 and 5 days	☐	☐
Between 6 and 10 days	☐	☐
For more than 10 days	☐	☐

C3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins? (*Please cross one box)*

None at all	☐
Between 1 and 5 days	☐
Between 6 and 10 days	☐
For more than 10 days	☐

C4. In the last two weeks, how much ankle swelling have you had? (*Please cross one box*)

None at all	☐
Slight ankle swelling	☐
Moderate ankle swelling (causing you to sit with your feet up whenever possible)	☐
Severe ankle swelling (causing you difficulty putting on your shoes)	☐

C5. In the last two weeks, have you worn support stockings or tights? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, those I bought myself without a doctor's prescription	☐	☐
Yes, those my doctor prescribed for me which I wear occasionally	☐	☐
Yes, those my doctor prescribed for me which I wear every day	☐	☐

C6. In the last two weeks, have you had any itching in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Both above and below the knee	☐	☐

C7. Do you have any purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C8. Do you have a rash or eczema in the area of your ankle? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes, but it does not require any treatment from a doctor or district nurse	☐	☐
Yes, and it requires treatment from my doctor or district nurse	☐	☐

C9. Do you have a skin ulcer associated with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C10. Does the appearance of your varicose veins cause you concern? (*Please cross one box*)

No	☐
Yes, their appearance causes me slight concern	☐
Yes, their appearance causes me moderate concern	☐
Yes, their appearance causes me a great deal of concern	☐

C11. Does the appearance of your varicose veins influence your choice of clothing including tights? (*Please cross one box*)

- ☐ No
- ☐ Occasionally
- ☐ Often
- ☐ Always

C12. During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities? (Please cross one box)

- ☐ No
- ☐ I have been able to work but my work has suffered to a slight extent
- ☐ I have been able to work but my work has suffered to a moderate extent
- ☐ My veins have prevented me from working one day or more

C13. During the last two weeks have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)? (*Please cross one box*)

- ☐ No
- ☐ Yes, my enjoyment has suffered to a slight extent
- ☐ Yes, my enjoyment has suffered to a moderate extent
- ☐ Yes, my veins have prevented me taking part in any leisure activities

SECTION D: YOUR SYMPTOMS

Listed below are a number of symptoms that you may or may not have experienced since you developed varicose veins.

Please indicate by crossing *Yes* or *No* whether you have experienced any of these symptoms since you developed varicose veins, and whether you believe that these symptoms are related to your varicose veins.

		I have experienced this symptom *since I developed varicose veins*		This symptom is *related to my varicose veins*	
D1.	Pain	Yes ☐	No ☐	Yes ☐	No ☐
D2.	Hardening of the skin on the legs	Yes ☐	No ☐	Yes ☐	No ☐
D3.	Redness of the skin on the legs	Yes ☐	No ☐	Yes ☐	No ☐
D4.	Sleep difficulties	Yes ☐	No ☐	Yes ☐	No ☐
D5.	Swelling of the ankle	Yes ☐	No ☐	Yes ☐	No ☐
D6.	Discolouration or brown staining on the leg	Yes ☐	No ☐	Yes ☐	No ☐
D7.	Stiff joints	Yes ☐	No ☐	Yes ☐	No ☐
D8.	Weight loss	Yes ☐	No ☐	Yes ☐	No ☐
D9.	Dizziness	Yes ☐	No ☐	Yes ☐	No ☐
D10.	Fatigue	Yes ☐	No ☐	Yes ☐	No ☐
D11.	Breaks in the skin or ulcers on the leg	Yes ☐	No ☐	Yes ☐	No ☐
D12.	Sore eyes	Yes ☐	No ☐	Yes ☐	No ☐
D13.	Breathlessness	Yes ☐	No ☐	Yes ☐	No ☐
D14.	Loss of strength	Yes ☐	No ☐	Yes ☐	No ☐

SECTION E: YOUR VIEWS ABOUT YOUR VARICOSE VEINS

We are interested in your own personal views of how you now see your varicose veins. Please indicate how much you agree or disagree with the following statements about your varicose veins by crossing the appropriate box.

Views about your varicose veins		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
E1.	My varicose veins will last a short time	☐	☐	☐	☐	☐
E2.	My varicose veins are likely to be permanent rather than temporary	☐	☐	☐	☐	☐
E3.	My varicose veins will last for a long time	☐	☐	☐	☐	☐
E4.	These varicose veins will pass quickly	☐	☐	☐	☐	☐
E5.	I expect to have these varicose veins for the rest of my life	☐	☐	☐	☐	☐
E6.	My varicose veins are a serious condition	☐	☐	☐	☐	☐
E7.	My varicose veins have major consequences on my life	☐	☐	☐	☐	☐
E8.	My varicose veins do not have much effect on my life	☐	☐	☐	☐	☐
E9.	My varicose veins strongly affect the way others see me	☐	☐	☐	☐	☐
E10.	My varicose veins have serious financial consequences	☐	☐	☐	☐	☐
E11.	My varicose veins cause difficulties for those who are close to me	☐	☐	☐	☐	☐
E12.	There is a lot which I can do to control my symptoms	☐	☐	☐	☐	☐

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
E13. What I do can determine whether my varicose veins get better or worse	☐	☐	☐	☐	☐
E14. The course of my varicose veins depends on me	☐	☐	☐	☐	☐
E15. Nothing I do will affect my varicose veins	☐	☐	☐	☐	☐
E16. I have the power to influence my varicose veins	☐	☐	☐	☐	☐
E17. My actions will have no effect on the outcome of my varicose veins	☐	☐	☐	☐	☐
E18. My varicose veins will improve in time	☐	☐	☐	☐	☐
E19. There is very little that can be done to improve my varicose veins	☐	☐	☐	☐	☐
E20. My treatment will be effective in curing my varicose veins	☐	☐	☐	☐	☐
E21. The negative effects of my varicose veins can be prevented (avoided) by my treatment	☐	☐	☐	☐	☐
E22. My treatment can control my varicose veins	☐	☐	☐	☐	☐
E23. There is nothing which can help my varicose veins	☐	☐	☐	☐	☐
E24. The symptoms of my varicose veins are puzzling to me	☐	☐	☐	☐	☐
E25. My varicose veins are a mystery to me	☐	☐	☐	☐	☐

Views about your varicose veins	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
E26. I don't understand my varicose veins	☐	☐	☐	☐	☐
E27. My varicose veins don't make any sense to me	☐	☐	☐	☐	☐
E28. I have a clear picture or understanding of my varicose veins	☐	☐	☐	☐	☐
E29. The symptoms of my varicose veins change a great deal from day to day	☐	☐	☐	☐	☐
E30. My symptoms come and go in cycles	☐	☐	☐	☐	☐
E31. My varicose veins are very unpredictable	☐	☐	☐	☐	☐
E32. I go through cycles in which my varicose veins get better and worse	☐	☐	☐	☐	☐
E33. I get depressed when I think about my varicose veins	☐	☐	☐	☐	☐
E34. When I think about my varicose veins I get upset	☐	☐	☐	☐	☐
E35. My varicose veins make me feel angry	☐	☐	☐	☐	☐
E36. My varicose veins do not worry me	☐	☐	☐	☐	☐
E37. Having these varicose veins makes me feel anxious	☐	☐	☐	☐	☐
E38. My varicose veins make me feel afraid	☐	☐	☐	☐	☐

SECTION F: CAUSES OF YOUR VARICOSE VEINS

We are interested in what you consider may have been the cause of your varicose veins. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your varicose veins rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your varicose veins. Please indicate how much you agree or disagree that they were causes for you by crossing the appropriate box.

Possible causes		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
F1.	Stress or worry	☐	☐	☐	☐	☐
F2.	Hereditary - it runs in my family	☐	☐	☐	☐	☐
F3.	A germ or virus	☐	☐	☐	☐	☐
F4.	Diet or eating habits	☐	☐	☐	☐	☐
F5.	Chance or bad luck	☐	☐	☐	☐	☐
F6.	Poor medical care in my past	☐	☐	☐	☐	☐
F7.	Pollution in the environment	☐	☐	☐	☐	☐
F8.	My own behaviour	☐	☐	☐	☐	☐
F9.	My mental attitude, e.g. thinking about life negatively	☐	☐	☐	☐	☐
F10.	Family problems or worries caused my varicose veins	☐	☐	☐	☐	☐
F11.	Overwork	☐	☐	☐	☐	☐
F12.	My emotional state, e.g. feeling down, lonely, anxious, empty	☐	☐	☐	☐	☐
F13.	Ageing	☐	☐	☐	☐	☐
F14.	Alcohol	☐	☐	☐	☐	☐
F15.	Smoking	☐	☐	☐	☐	☐
F16.	Accident or injury	☐	☐	☐	☐	☐
F17.	My personality	☐	☐	☐	☐	☐
F18.	Altered immunity	☐	☐	☐	☐	☐

In the table below, please list in rank-order the three most important factors that you now believe caused your illness. You may use any of the items from the box above, or you may have additional ideas of your own.

The most important causes for me:-

1. _____

2. _____

3. _____

SECTION G: YOUR MOST RECENT ADMISSION TO HOSPITAL

This section of the questionnaire will help us to find out how much it costs you to use health services. We will ask about your most recent admission to hospital, your most recent outpatient appointment and your most recent appointment with a GP. We wish to know how much money and time were spent by you and any companion in attending these appointments and as a result of any hospital admission you may have had.

If, in the last 6 months, you were **not** admitted to hospital please go to **Section H.**

G1. Please cross the box that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

Bus	☐	Hospital car	☐
Train	☐	Ambulance	☐
Taxi	☐	Other (please specify below)	☐
Private car	☐		

_____

G2. **If you travelled by bus, train or taxi to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare.**

Cost of (one-way) fare (£) ☐☐ – ☐☐ pence

G3. **If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.**

Number of miles one-way ☐☐☐

G4. **If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay a parking fee.**

Expenditure on parking fee (£) ☐☐ – ☐☐ pence

G5. **When you were admitted to the hospital, how long did you spend there? Please write the number of days in the box below.**

Number of days ☐☐

G6. **What would you otherwise have been doing as your main activity if you had not had to be admitted to hospital? Please cross the box that best applies to you.**

Paid work	☐	Unemployed	☐
Housework	☐	Voluntary work	☐
Childcare	☐	Leisure activities	☐
Caring for a relative or friend	☐	Other (please specify below)	☐

G7. When you were admitted to hospital, did anyone come with you?

Yes ☐ Go to **G8**

No ☐ Go to **Section H**

G8. Who accompanied you to the hospital? Please cross the box that best describes the main person who accompanied you to the hospital.

Partner/spouse	☐	Paid caregiver	☐
Other relative	☐	Other (please specify below)	☐
Friend	☐		

_____

G9. Please cross the box that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the hospital.

Paid work	☐	Unemployed	☐
Housework	☐	Voluntary work	☐
Childcare	☐	Leisure activities	☐
Caring for a relative or friend	☐	Other (please specify below)	☐

_____

G10. Did your main companion take time off from paid work (or business activity if self-employed)?

Yes ☐ Go to **G11**

No ☐ Go to **Section H**

G11. Please write the number of hours your companion took off from paid work (or business activity if self-employed) in the box below. Please put zero if your main companion did not take time off from paid work (or business activity if self-employed) to accompany you to the hospital.

Number of hours ☐☐

G12. Whilst you were in hospital, approximately how many times did your main companion come to visit you?

Number of times ☐☐

SECTION H: YOUR MOST RECENT OUTPATIENT VISIT

If, in the last 6 months, you did **not** have an outpatient's appointment, please go to **Section I.**

H1. Please cross the box that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

Bus	☐	Hospital car	☐
Train	☐	Ambulance	☐
Taxi	☐	Other (please specify below)	☐
Private car	☐		

_____

H2. If you travelled by bus, taxi or train to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare.

Cost of (one-way) fare (£) ☐☐ – ☐☐ pence

H3. **If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.**

Number of miles one-way ☐☐☐

H4. **If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay a parking fee.**

Expenditure on parking fee (£) ☐☐ – ☐☐ pence

H5. **When you visited outpatients, how long did it take to travel there? Please write the number of hours and minutes in the box below.**

Number of hours ☐☐ – ☐☐ minutes

H6. **When you visited outpatients, how long did you spend there? Please write the number hours and minutes in the box below.**

Number of hours ☐☐ – ☐☐ minutes

H7. **Please cross the box that best describes what you otherwise would have been doing as your main activity if you had not been visiting outpatients?**

Paid work	☐	Unemployed	☐
Housework	☐	Voluntary work	☐
Childcare	☐	Leisure activities	☐
Caring for a relative or friend	☐	Other (please specify below)	☐

H8. When you visited outpatients did anyone come with you?

Yes ☐ Go to **H9**

No ☐ Go to **Section I**

H9. Please cross the box that best describes the main person who accompanied you to outpatients.

Partner/spouse	☐	Paid caregiver	☐
Other relative	☐	Other (please specify below)	☐
Friend	☐		

_____

H10. If your main companion travelled with you by bus or train approximately how much did they pay (one-way) in fares? Please write the approximate cost in the box below. Please put zero if your main companion did not travel by bus or train at all.

Cost of (one-way) fare (£) ☐☐ – ☐☐ pence

H11. Please cross the box that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to outpatients.

Paid work	☐	Unemployed	☐
Housework	☐	Voluntary work	☐
Childcare	☐	Leisure activities	☐
Caring for a relative or friend	☐	Other (please specify below)	☐

_____

SECTION I: YOUR MOST RECENT GP APPOINTMENT

I1. Please cross the box that best describes how you travelled to your most recent GP appointment. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

Walked	☐	Bus	☐
Cycled	☐	Taxi	☐
Private car	☐	Other (please specify below)	☐

_____

I2. If you travelled by bus or taxi, what was the cost of the (one-way) fare? Please write the cost in the box below. Please put zero if you did not travel by bus or taxi or if you did not pay the fare.

Cost of (one-way) fare (£) ☐☐ – ☐☐ pence

I3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.

Number of miles one-way ☐☐☐

I4. If you travelled by private car and you or a companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay for parking.

Expenditure on parking fee (£) ☐☐ – ☐☐ pence

I5. When you visited the GP, how long did it take to travel there? Please write the number of minutes in the box below.

Number of minutes ☐☐☐

I6. When you visited the GP, how long did you spend there? Please write the number minutes in the box below. Please include in your answer the time spent waiting and also the time spent with the doctors and nurses

Number of minutes ☐☐☐

I7. Please cross the box that best describes what you otherwise would have been doing as your main activity if you had not visited the GP.

Paid work	☐	Unemployed	☐
Housework	☐	Voluntary work	☐
Childcare	☐	Leisure activities	☐
Caring for a relative or friend	☐	Other (please specify below)	☐

_____

I8. When you visited the GP did anyone come with you?

Yes ☐ Go to **I9**

No ☐ Go to **Section J**

I9. Please cross the box(es) that best describe the person(s) who accompanied you to the GP surgery.

Partner/spouse	☐	Paid caregiver	☐
Other relative	☐	Other (please specify below)	☐
Friend	☐		

_____

I10. If your main companion travelled with you by bus how much approximately did they pay (one-way) in fares (if anything)? Please write the cost in the box below. Please put zero if your main companion did not travel by bus at all.

Cost of (one-way) fare (£) ☐☐ – ☐☐ pence

I11. Please cross the box that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the GP's surgery.

Paid work	☐	Unemployed	☐
Housework	☐	Voluntary work	☐
Childcare	☐	Leisure activities	☐
Caring for a relative or friend	☐	Other (please specify below)	☐

_____

SECTION J: HEALTH SERVICE UTILISATION QUESTIONNAIRE

Please try to complete all the questions. Most questions can be answered by putting numbers or a cross in the appropriate boxes. In a few questions you are asked to write some details. This set of questions is about any appointments you may have had with a general practice in the past 6 months.

J1. Have you been to see a GP because of your varicose veins during the last 6 months?

Yes	No
☐	☐

If **Yes**, please give details:

How many appointments did you attend with a GP because of your varicose veins? ☐☐

How many times did a GP visit you at home because of your varicose veins? ☐☐

How many times did you have a telephone conversation with a GP because of your varicose veins? ☐☐

J2. Please make a list below of all the medication you currently take:

This set of questions is about any appointments you may have had with other health care workers in the past 6 months.

J3. During the last 6 months have you had an appointment with any of these care providers because of your varicose veins:

A District Nurse? Yes ☐ No ☐

If **Yes**, how many appointments have you had? ☐☐

A Practice Nurse? Yes ☐ No ☐

If **Yes**, how many appointments have you had? ☐☐

An NHS physiotherapist? Yes ☐ No ☐

If **Yes**, how many appointments have you had? ☐☐

An Occupational Therapist? Yes ☐ No ☐

If **Yes**, how many appointments have you had? ☐☐

Other? (*please specify below*) Yes ☐ No ☐

_____

How many appointments have you had? ☐☐

_____

How many appointments have you had? ☐☐

This set of questions is about any private health care you may have had in the past 6 months

J4. During the last 6 months have you paid for any private health care for your varicose veins?

Yes ☐ No ☐

If **Yes**, what sort of care did you pay for?

_____

_____

If **Yes**, and you had appointments, how many appointments did you have? ☐☐

If you wish to provide further information please do so in the box below.

THANK YOU

Thank you very much for your time and patience in filling in this questionnaire. Please hand the questionnaire back to the nurse or return it in the enclosed reply-paid envelope to the Trial Office in Aberdeen.

The information you have given us will be extremely useful in helping us carry out research. It will be treated with the strictest confidence and kept securely.

Thank you again for your help

If you would like any further information or have any queries about the study, please contact:

The CLASS Trial Office in Aberdeen (Tel: 01224 XXXXXX)

This study is taking place across the UK but the questionnaires are being processed in Aberdeen at The Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, Health Sciences Building, Foresterhill, ABERDEEN, AB25 2ZD.

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

CASE NOTE DATA ABSTRACTION FORM: USE OF SERVICES

(Use of hospital services from discharge following index admission until the end of the last day of follow-up)

Study Number | | | | | | |

Date randomised D D / M M / Y Y Y Y

Last day of follow-up D D / M M / Y Y Y Y

1. Has the patient been admitted to hospital?

Yes ☐ No ☐

If Yes, please give details below

Specialty	Date admitted	Date discharged
e.g. general surgery	22/07/2008	08/08/2008
	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y

2. Has the patient had another operation?

Yes ☐ No ☐

If Yes, please give details below

Specialty	Date admitted	Date discharged
e.g. general surgery	22 / 07 / 2008	08 / 08 / 2008
	DD / MM / YYYY	DD / MM / YYYY
	DD / MM / YYYY	DD / MM / YYYY
	DD / MM / YYYY	DD / MM / YYYY
	DD / MM / YYYY	DD / MM / YYYY
	DD / MM / YYYY	DD / MM / YYYY

3. Has the patient had any outpatient visits to the following specialties/departments?

Surgical	Yes ☐ No ☐	If Yes, how many visits?	
Ear, Nose & Throat	Yes ☐ No ☐	If Yes, how many visits?	
Medical	Yes ☐ No ☐	If Yes, how many visits?	
Sexual Medicine/Urology	Yes ☐ No ☐	If Yes, how many visits?	
Physiotherapy	Yes ☐ No ☐	If Yes, how many visits?	
Occupational Therapy	Yes ☐ No ☐	If Yes, how many visits?	
Dietician	Yes ☐	If Yes, how many visits?	

	No ☐		
Pain Team	Yes ☐	If Yes, how many visits?	
	No ☐		
Other?	Yes ☐	*If yes*, please specify below	
	No ☐		
		How many visits?	
		How many visits?	

CLASS

Comparison of LAser, Surgery and foam Sclerotherapy

SERIOUS ADVERSE EVENT REPORT

To be completed for any serious adverse event, whether they are expected or unexpected, related or unrelated.

An event is deemed "serious" if the patient died; it involved or prolonged inpatient hospitalization; it involved persistent or significant disability or incapacity; was life threatening; or resulted in congenital anomaly or birth defect.

The events defined as expected are deep vein thrombosis, pulmonary embolism, anaphylactic shock, stroke, retinal arteriole occlusion, myocardial infarction, cutaneous necrosis and ulceration, epileptic fit, intra-arterial injection, injury to a major artery (common femoral or superficial femoral), injury to a major vein (common femoral or popliteal), injury to a motor nerve (femoral, tibial or peroneal), transient ischemic attack.

A. Patient Details

Hospital number | Study No. | | | | | | |

Patient's initials |

Date of birth | D D / M M / Y Y Y Y |

Age |

Sex | Male ☐ | Female ☐

Treating Hospital |

B. Adverse Event

Place where adverse event took place / detected |

Date of event | D D / M M / Y Y Y Y |

Brief details of adverse event |

Date of report | D D / M M / Y Y Y Y |

C. Cross all boxes appropriate to adverse event.

If any box is crossed the adverse event is serious

- Patient died ☐
- Involved or prolonged inpatient hospitalisation ☐
- Involved persistent or significant disability or incapacity ☐
- Life threatening ☐
- Congenital anomaly/birth defect ☐
- 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 above ☐

D. What treatment for varicose veins had the patient received?

Laser treatment ☐ Date(s) of procedure D D / M M / Y Y Y Y

D D / M M / Y Y Y Y

Surgery ☐ Date(s) of procedure D D / M M / Y Y Y Y

D D / M M / Y Y Y Y

Foam sclerotherapy ☐

Date(s) and dose(s) of Fibrovein administered

		Concentration	Volume of foam	Batch number
1.	D D / M M / Y Y Y Y	%	ml	
2.	D D / M M / Y Y Y Y	%	ml	
3.	D D / M M / Y Y Y Y	%	ml	
4.	D D / M M / Y Y Y Y	%	ml	

Route of administration: Intravenous

Indication(s) for use: Treatment of varicose veins (in CLASS trial)

E. Was the adverse event 'expected'?

Is this serious adverse event one of:

- Deep vein thrombosis [*following foam, laser, surgery*]
- Pulmonary embolism [*following foam, laser, surgery*]
- Anaphylactic shock [*following foam*]
- Stroke [*following foam*]
- Retinol arterial occlusion [*following foam*]
- Myocardial infarction [*following foam*]
- Cutaneous necrosis and ulceration [*following foam*]
- Epileptic fit [*following foam*]
- Intra-arterial injection [*following foam*]
- Injury to a major artery (common femoral or superficial femoral) [*following surgery*]
- Injury to a major vein (common femoral or popliteal) [*following foam, laser, surgery*]
- Injury to a motor nerve (femoral, tibial or peroneal) [*following surgery*]
- Transient Ischemic Attack [*following foam*]

and therefore an "expected" serious adverse event?

Yes ☐

No ☐ If NO, this could be a SUSAR

F. Concomitant drug(s) and history

Concomitant drug(s) and dates of administration (exclude those used to treat reaction)	
Other relevant history (e.g. diagnostics, allergies etc)	

G. Assessment of whether event was caused by study intervention

Is it reasonably likely that adverse event was caused by the study intervention?

Yes ☐ No ☐

Why?

Name and position of person making this judgement

Date of assessment D D / M M / Y Y Y Y

Any subsequent information

H. Contact details for person initially reporting adverse event

Name

Address

Telephone

Email

I. Manufacturing and packaging information for fibrovein
Complete only if patient received foam sclerotherapy

Name and address of manufacturer

CP Pharmaceuticals Ltd
Wrexham Industrial Estate, Wrexham, Clwyd, LL13 9UF

Date report sent to manufacturer D D / M M / Y Y Y Y

Appendix 2 Additional trial results tables

TABLE 106 Pain scores during treatment and at 6 weeks following treatment: comparison of foam sclerotherapy with surgery

	Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. foam sclerotherapy[a]		
Pain VAS scores	*n*	Mean	SD	*n*	Mean	SD	Effect size	95% CI	*p*-value
Pain VAS scores completed immediately after treatment	226	2.2	1.9	163	2.3	2.6	0.06	–0.38 to 0.50	0.796
Pain VAS scores completed at 6 weeks									
During treatment	240	3.0	2.4	227	4.0	3.0	1.04	0.57 to 1.52	< 0.001
During recovery	239	3.0	2.4	229	4.3	2.8	1.21	0.76 to 1.66	< 0.001

a Where the effect size is positive, this favours foam sclerotherapy.

TABLE 107 Pain scores during treatment and at 6 weeks following treatment: comparisons of EVLA with foam sclerotherapy, and surgery with EVLA

	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery			Surgery vs. EVLA			EVLA vs. foam		
Pain VAS scores	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Effect size	95% CI	*p*-value	Effect size	95% CI	*p*-value
Pain VAS scores completed immediately after treatment	171	3.5	2.2	170	2.2	2.0	137	2.4	2.6	−1.12	−1.61 to −0.62	< 0.001	1.25	0.79 to 1.72	< 0.001
Pain VAS scores completed at 6 weeks															
Pain during treatment	178	4.4	2.8	176	3.0	2.5	165	4.1	3.0	−0.23	−0.78 to 0.33	0.418	1.40	0.86 to 1.95	< 0.001
Pain during recovery	178	3.4	2.6	176	2.8	2.3	166	4.2	2.7	0.79	0.28 to 1.30	0.002	0.60	0.10 to 1.11	0.019

TABLE 108 Illness perception: comparison of foam sclerotherapy with surgery

Illness perception component	Randomised to foam sclerotherapy			Randomised to surgery		
Identity score						
Baseline (*n*, mean, SD)	265	2.6	1.5	274	2.9	1.6
Post randomisation (*n*, mean, SD)	137	2.7	1.5	117	3.1	1.6
6 months (*n*, mean, SD)	212	2.4	1.6	179	2.1	1.7
Percentage of symptoms correctly identified as being related to varicose veins						
Baseline (*n*, mean, SD)	263	74.7%	29.8%	274	75.2%	27.4%
Post randomisation (*n*, mean, SD)	136	79.3%	27.1%	121	78.3%	25.8%
6 months (*n*, mean, SD)	205	82.1%	27.2%	154	77.1%	31.4%
Timeline acute/chronic						
Baseline (*n*, mean, SD)	280	23.7	4.8	280	23.6	4.5
Post randomisation (*n*, mean, SD)	142	23.5	4.6	125	23.8	4.8
6 months (*n*, mean, SD)	228	21.0	5.2	196	21.2	5.1
Timeline cyclical						
Baseline (*n*, mean, SD)	279	10.7	3.4	280	10.9	3.2
Post randomisation (*n*, mean, SD)	142	10.5	3.1	126	11.0	3.3
6 months (*n*, mean, SD)	228	9.6	3.2	199	9.9	3.2
Consequences						
Baseline (*n*, mean, SD)	281	15.9	4.2	281	16.1	4.4
Post randomisation (*n*, mean, SD)	142	16.1	4.0	126	15.6	4.3
6 months (*n*, mean, SD)	227	13.6	4.0	196	13.9	4.1
Personal control						
Baseline (*n*, mean, SD)	279	18.6	4.2	279	18.3	3.8
Post randomisation (*n*, mean, SD)	142	18.7	3.8	126	18.4	4.2
6 months (*n*, mean, SD)	227	19.0	4.2	197	18.9	4.1
Treatment control						
Baseline (*n*, mean, SD)	279	19.5	2.5	278	19.3	2.3
Post randomisation (*n*, mean, SD)	141	19.1	2.5	126	19.0	2.3
6 months (*n*, mean, SD)	227	18.8	2.8	197	18.4	2.9
Illness coherence						
Baseline (*n*, mean, SD)	276	17.7	4.1	277	17.6	3.7
Post randomisation (*n*, mean, SD)	142	17.9	4.1	125	18.2	4.2
6 months (*n*, mean, SD)	225	18.2	3.8	196	18.6	3.9
Emotional representations						
Baseline (*n*, mean, SD)	281	15.4	4.5	280	14.9	4.7
Post randomisation (*n*, mean, SD)	142	15.6	4.5	126	15.1	5.0
6 months (*n*, mean, SD)	228	13.4	4.6	200	13.5	4.3

TABLE 109 Illness perception: comparisons of EVLA with foam sclerotherapy, and surgery with EVLA

Illness perception	Randomised to EVLA			Randomised to foam sclerotherapy			Randomised to surgery		
Identity score									
Baseline (*n*, mean, SD)	195	2.7	1.5	193	2.6	1.6	202	2.9	1.5
Post randomisation (*n*, mean, SD)	84	2.9	1.7	88	2.6	1.5	73	3.1	1.7
6 months (*n*, mean, SD)	141	2.2	1.7	149	2.3	1.6	125	2.1	1.7
Percentage of symptoms correctly identified as being related to varicose veins									
Baseline (*n*, mean, SD)	200	72.4%	31.1%	193	73.8%	30.1%	201	75.1%	28.4%
Post randomisation (*n*, mean, SD)	83	75.8%	27.8%	87	78.7%	27.6%	77	77.1%	27.1%
6 months (*n*, mean, SD)	133	79.0%	32.5%	147	79.6%	29.2%	108	74.2%	33.1%
Timeline acute/chronic									
Baseline (*n*, mean, SD)	209	23.6	4.7	206	23.4	4.8	206	23.1	4.5
Post randomisation (*n*, mean, SD)	90	23.1	4.7	92	23.4	4.7	80	23.4	4.5
6 months (*n*, mean, SD)	161	20.6	4.8	166	20.8	5.1	141	21.0	5.1
Timeline cyclical									
Baseline (*n*, mean, SD)	208	10.5	3.3	203	11.1	3.3	209	11.0	3.3
Post randomisation (*n*, mean, SD)	90	10.4	3.0	92	10.7	3.1	81	11.1	3.5
6 months (*n*, mean, SD)	159	9.5	3.1	164	9.7	3.1	144	10.1	3.2
Consequences									
Baseline (*n*, mean, SD)	209	16.4	4.3	206	16.2	4.3	207	16.0	4.2
Post randomisation (*n*, mean, SD)	90	16.0	3.6	92	16.0	3.8	81	15.7	4.7
6 months (*n*, mean, SD)	160	13.8	3.6	165	13.6	3.9	141	14.0	4.0
Personal control									
Baseline (*n*, mean, SD)	209	18.5	4.1	205	18.7	4.1	206	18.6	3.7
Post randomisation (*n*, mean, SD)	89	18.7	4.1	92	18.6	3.9	81	18.7	4.3
6 months (*n*, mean, SD)	158	18.9	3.9	165	19.3	4.1	142	19.3	4.1
Treatment control									
Baseline (*n*, mean, SD)	209	19.6	2.3	205	19.3	2.5	205	19.3	2.3
Post randomisation (*n*, mean, SD)	90	19.2	2.0	91	18.9	2.3	81	18.9	2.2
6 months (*n*, mean, SD)	157	18.8	2.5	165	18.8	2.5	142	18.3	3.0
Illness coherence									
Baseline (*n*, mean, SD)	208	17.4	3.8	203	17.4	4.1	206	17.5	3.7
Post randomisation (*n*, mean, SD)	90	17.8	3.8	92	17.3	4.2	81	17.6	4.3
6 months (*n*, mean, SD)	156	17.9	3.3	163	17.7	3.9	141	18.4	3.8
Emotional representations									
Baseline (*n*, mean, SD)	208	16.1	4.7	205	15.7	4.5	209	14.9	4.6
Post randomisation (*n*, mean, SD)	90	16.2	4.8	92	15.6	4.4	81	15.4	5.4
6 months (*n*, mean, SD)	159	13.6	4.2	164	13.5	4.5	145	13.5	4.6

Appendix 3 Behavioural Recovery After treatment for Varicose Veins study paperwork

The BRAVO Study

NHS Grampian

Vascular Department, Ward 36
Aberdeen Royal Infirmary
Aberdeen

Dear

A STUDY OF PATIENTS' VIEWS ON RECOVERY FROM TREATMENT FOR VARICOSE VEINS

We approached you today to ask if you would be willing to take part in a discussion group. In these discussion groups we are speaking to people who have recently had treatment for varicose veins to find out about what was important to them during in their recovery. The discussion group would take place in a few weeks time. For a couple of days after the discussion group we are asking participants to fill in a diary. As you have recently been treated for varicose veins, we are asking you to consider participating and sharing your views.

We enclose a leaflet giving you further information about the study. It explains why the study is being done and what you would need to do if you were willing to take part in the study. After you have read this letter and the information leaflet, if you would like to take part, please fill in the form at the bottom of this letter and return it in the envelope provided (no stamp is needed). Travelling expenses to and from the discussion group will be reimbursed, together with any parking or child-care costs. If you would like to participate but cannot travel to the discussion group (which would be held in Aberdeen) we would still like to speak with you and get your opinions by telephone or in a face-to-face interview.

Although we would be very pleased if you did join a discussion group or agree to be interviewed, we stress that you are under no obligation to participate in the study.

If you have any questions about the study, please contact the researcher by telephone on 01224 XXXXXX or myself on 01224 XXXXXX.

Yours sincerely

Dr Julie Brittenden

✂----------

Name .....

Address .....

Tel no .....

Yes, I would like to take part in a discussion group or an interview. I give permission for a member of the research team to contact me to arrange this. ☐

Please return this in the envelope provided. No stamp is needed.

Health Services Research Unit

University of Aberdeen
3rd Floor
Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD
Scotland
United Kingdom

Tel: 44 (0) 1224 XXXXXX
Fax: 44 (0) 1224 XXXXXX
Email:

The BRAVO Study

A STUDY OF PATIENTS' VIEWS ON RECOVERY FROM TREATMENT FOR VARICOSE VEINS

Patient Information Leaflet

Introduction

You are being invited to take part in a research study. In this study, we are interviewing people who have recently had treatment for varicose veins to find out about what was important to them during their recovery. As you have had treatment for varicose veins, we are asking you to consider participating and sharing your views. We are using the information from the interviews to develop a questionnaire to use in another research study of people having treatment for varicose veins. Collecting information from people like yourself who have had treatment for varicose veins will help us make sure that this questionnaire will ask the appropriate questions.

Information sheet for patients approached at clinic, Version 1, 21 August 2008

What is the purpose of this study?
As someone who has recently had treatment for varicose veins, you might be able to help us. We are keen to hear from people like you about their experiences and thoughts about the treatment and their recovery.

The information from interviews and discussion groups will tell us what is important for people during their recovery from treatment for varicose veins. From this information, we will develop a questionnaire to use in a larger study of treatments for varicose veins.

What will I have to do to take part?
If you agree to take part in our study, we would ask you to participate in a discussion group with between five and seven other people who have had treatment for varicose veins. In total, we hope that approximately twenty-one people will take part in this study. The discussion group would take place a few weeks after your treatment.

A member of the study team will lead the discussion group and ask some questions. The discussion will last about one hour and thirty minutes, and will include a refreshment break. The discussion will take place in the Health Sciences Building which is on the Foresterhill site, and travel, parking and child-care expenses will be reimbursed.

The discussion will be tape-recorded. The tape recording will be treated confidentially.

If you want to take part in the study but cannot manage to attend a discussion group, it might be possible to organise a one-to-one interview with you, either in person or over the telephone.

After the discussion group or interview we will ask you to fill in a diary for a couple of days. We will give you a pre-paid envelope to return this to the study office.

What will be done with what I say?
We will use the transcript of the discussion to create a summary of all the opinions that were expressed. The tape and transcript will be stored safely and will be destroyed after the end of the study.

The only people who will be able to hear the tape-recorded discussion will be the research team and a secretary at the Health Services Research Unit at the University of Aberdeen (who will transcribe the tape). No information will be published that could identify you.

What will be done with what I write in my diary?
We will create a summary of the information contained in all the diaries. The diary will be stored safely and destroyed at the end of the study.

What are the possible risks of taking part?
We do not think that taking part in the discussion will have any risks for your health. Your health care will not be affected.

What are the possible benefits of taking part?
We hope that you will enjoy taking part in the discussion. You might find it interesting to meet and talk with other people who have had treatment for varicose veins. By participating in a discussion, you will also be helping the research team to understand issues from the perspectives of people who have had treatment for varicose veins. If you enjoy taking part in this research, there may be an opportunity for you to continue advising the research team by joining our panel of service users.

Will I be able to find out the results of the study?
If you wish, the researcher will send you a written summary of the findings.

Do I have to take part?
No. If you do not want to take part in a discussion that is fine. You do not have to give a reason. If you agree to join a discussion group, but later change your mind, you can withdraw your consent at any time. Your care will not be affected.

What should I do if I do NOT want to take part?
If you do not want to take part in a discussion, you do not need to do anything. Thank you for reading about the study.

What should I do if I DO wish to take part?
If you might like to take part in a discussion group, you can let us know by filling in the form at the bottom of your letter, and returning it to us in the envelope provided (you do not need a stamp). If you do participate we will ask you to sign a consent form when you come to the discussion group. You will be given a copy of this consent form to keep.

Who has reviewed the study?
This study has been reviewed by the research team and the North of Scotland Research Ethics Committee.

Any questions?
If you have any questions at all about the study, you can contact a member of the research team on the telephone numbers below.

Health Services Research Unit

University of Aberdeen
3rd Floor
Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD
Scotland
United Kingdom

Tel: 44 (0) 1224 XXXXXX
Fax: 44 (0) 1224 XXXXXX
Email: xxxxxxx@abdn.ac.uk

The BRAVO Study

A study of patients' views on recovery from treatment for varicose veins

Study No ☐☐☐

CONSENT FORM

Name of Researcher: _____

PLEASE INITIAL BOX

1. I confirm that I have read and understand the information sheet dated May 2008 (version 1) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the discussions I have about the study may be tape recorded but that these will be kept confidentially and I will not be identified individually. ☐
4. I agree to take part in the study on views of patients about recovery from treatment for varicose veins. ☐

Name of patient	Date	Signature
Name of person taking consent	Date	Signature

1 for patient; 1 for researcher

INTERVIEW TOPIC GUIDE, BRAVVO STUDY

1. Introductions and Review
   - Introduce people in the room
   - Objective of BRAVVO study
   - What is asked of participants inc length of interview
   - Intention to audiotape
   - Confidentiality procedures
   - Participants' rights – to withdraw, ask for tape to be switched off etc

2. Check
   - Any questions
   - Procedures for reimbursement of costs

3. Sound check
   - Audibility of tape
   - Sound quality of each participant's voice (for transcriber)

4. Interview

Let's begin. First of all can you please tell us about your experience of the treatment itself.
(PROMPTS - Can you remember…
   - What happened?
   - Who was there?
   - How you felt?
   - How you were told to care for the leg after treatment?
   - How long after the treatment did you keep the support stockings on for?

As I've said, we are interested in the **milestones** you have achieved throughout your recovery from treatment.

A. So can you tell us some of the *things that you looked forward to doing for the first time* immediately after your treatment for varicose veins?
(PROMPTS AS NEEDED PRESENTED AS DOT POINTS BELOW):
   - While you were still at the hospital? After you returned home?
   - After the first week?
   - Anything that you had not been able to do before your treatment?
   - When did you do these activities – how long after your treatment?

B. Are there any activities that you *were worried about doing for the first time* after your treatment?
   - What activities were painful?
   - Were there any activities that you were worried might do damage?
   - When did you do these activities – how long after your treatment?
   - What happened when you did them?

C. Are there any activities that you *felt particularly pleased that you had achieved when you did them for the first time, after your treatment?*
   - When did you do these activities – how long after your treatment?
   - How did it feel?

D. You all had treatment a few weeks ago – is that right? Are there any *further milestones that you are still looking forward to doing or expecting to do* that you've not been able to do yet?
   - Anything else?

E. Is there anything else you remember about your recovery that you would like to mention?

Thank you very much for your help. I will also be talking to patients who had different treatments and we will write to you to let you know what we find out in this study. If you have got any comments about the focus group, or anything else about your treatment or recovery that you would like to tell us about, there are feedback sheets on the table. You can fill one of these in now, or if you want to take a copy home we will give you a reply paid envelope to send them back

Appendix 4 Resource use and costing questionnaire

Questionnaire to be completed by a member of staff familiar with the details of alternative procedures.

Section A: Endovenous Laser Ablation (EVLA)

1. What is the general location of this procedure e.g. clinic/theatre?_____

If theatre is the usual location, please answer the following questions:

2. On average, how long (in minutes) do patients spend on the day/short stay ward, prior to the procedure? _____

3. How many patients are generally on the day/short stay ward at any one time? _____

4. How long (in minutes) does the patient generally spend on the day/short stay ward post procedure?_____

If clinic is the usual location, please answer the following question:

5. Please specify the area where the patient goes to recover post procedure (e.g. reception)? _____

Please answer the following questions regarding both theatre and clinic settings:

6. Please complete the following table relating to staff present in theatre/clinic for the procedure:

Staff	Band	No. present	Any Comments
e.g. General Nurse	Salary band	Number of staff present	-

7. Please complete the following table which relates to major consumable items used for EVLA:

Consumable	Yes/No	Unit Cost	Any Comments
e.g. Laser Fibre			

8. Please complete the following table relating to capital equipment required for EVLA:

Capital Equipment	Make and model	Expected Useful Lifespan (years)	Unit cost	Number of patients it is used for each year
e.g. Laser Machine				

Section B: Foam Sclerotherapy

1. What is the general location of this procedure e.g. clinic/theatre?_____

2. Please specify the area where the patient goes to recover post procedure e.g. reception?
_____

3. Please complete the following table relating to staff present at the procedure:

Staff	Band	No. present	Any Comments
e.g. General nurse	Salary band	Number of staff present	

4. Please complete the following table relating to consumables used for foam sclerotherapy:

Consumable	Yes/No	Cost	Any Comments
e.g. Micropuncture kit			

5. Please complete the following table relating to capital equipment used for foam sclerotherapy:

Capital Equipment	Make and model	Expected Useful Lifespan	Unit cost	Number of patients it is used for each year
e.g. Ultrasound Machine (portable scanner)				

Section C: Surgery in a day case setting under local anaesthetic

1. On average, how long (in minutes) do patients spend on the day/short stay ward, prior to the procedure?_____

2. How many patients are generally on the day/short stay ward at any one time?_____

3. How long does the patient generally spend on the day/short stay ward post procedure?
_____

4. Please complete the following table relating to staff present in theatre:

Staff	Band	No. present	
e.g. General nurse	Salary band	Number of staff present	-

5. Please complete the following table relating to major consumable items used for surgery:

Consumable	Yes/No	Unit Cost	Any Comments
e.g. Disposable vein stripper			

Section D: Surgery in a day case setting under general anaesthetic

1. On average, how long (in minutes) do patients spend on the day/short stay ward, prior to the procedure?_____

2. How many patients are generally on the day/short stay ward at any one time?_____

3. How long (in minutes) does a patient generally spend on a recovery ward post procedure? _____

4. How many patients are generally on the recovery ward at any one time?_____

5. How many nurses generally staff the recovery ward?_____

6. How long (in minutes) does the patient spend on the day/short stay ward, after leaving the recovery ward, prior to discharge?_____

7. Please complete the following table relating to staff present during surgery in theatre:

Staff	Band	No. present	Any Comments
e.g. General nurse	Salary band	Number of staff present	-

8. Please complete the following table relating to major consumable items used for surgery:

Consumable	Yes/No	Unit Cost	Any Comments
e.g. Disposable vein stripper			

9. Please complete the following table relating to equipment required for surgery:

Equipment item	Yes/No	Make and model	Lifespan in years	Unit Cost	No of patients it is used for each year
e.g. Pulse oximeter					

EME
HS&DR
HTA
PGfAR
PHR

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