National Clinical Guideline Centre

Draft for consultation

Varicose veins in the legs

The diagnosis and management of varicose veins

Clinical guideline

Methods, evidence and recommendations

12 February 2013

Draft for consultation

Commissioned by the National Institute for Health and Clinical Excellence

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Funding
National Institute for Health and Clinical Excellence

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Acknowledgments

The development of this guideline was greatly assisted by the following people:

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1 Introduction

Varicose veins are dilated, often palpable subcutaneous veins with reversed blood flow, most commonly found in the legs. Estimates of the prevalence of varicose veins vary. Visible varicose veins in the lower limbs are estimated to affect at least a third of the population. There is little reliable information available in the literature on the proportion of people with varicose veins who progress to venous ulceration. One study reported that 28.6% of those who had visible varicose veins without oedema or other complications progressed to more serious venous disease after 6.6 years.[80] However there was no information about the numbers progressing to ulceration. Other data on the lifetime prevalence of varicose veins estimate that approximately 3-6% of people who have varicose veins in their lifetime will develop venous ulcers.[68] Risk factors for developing varicose veins are unclear although prevalence rises with age and they often develop during pregnancy. In some people varicose veins are asymptomatic or cause only mild symptoms, but in others they cause pain, aching or itching and can have a significant effect on their quality of life. Varicose veins may become more severe over time and can lead to complications such as changes in skin pigmentation, eczema, superficial thrombophlebitis, bleeding, loss of subcutaneous tissue, lipodermatosclerosis or venous ulceration. It is not known which people with varicose veins will develop more severe disease but it is estimated that 3-6% of people with varicose veins in their lifetime will develop venous ulcers.

There are several options for the management of varicose veins, including:

- advice and reassurance
- compression hosiery
- interventional treatments

Interventional treatments include surgery, foam sclerotherapy and endothermal ablation. Surgery is a traditional treatment that involves surgical removal by 'stripping' out the vein or ligation (tying off the vein). In foam sclerotherapy sclerosant foam (irritating agent) is injected into the vein to cause an inflammatory response which consequently closes it. There are two main endothermal methods: radiofrequency and laser ablation, these methods heat the vein from inside causing irreversibly damage to the vein and its lining and so closes it off. All treatments may be performed under general or local anaesthesia and do not usually require an overnight stay in hospital.

A review of the data from the trials of interventional procedures indicates that the rate of clinical recurrence of varicose veins at 3 years after treatment is likely to be between 10-30%. One of the aspects which prevents being able to provide clear figures on retreatment rates is the fact that many of the treatments are relatively new and the long term rates have not yet been published.

In 2009/10 there were 35,659 varicose veins procedures carried out in the NHS indicating a considerable financial cost and impact on workload. There is no clear simple system to identify which people benefit the most from interventional therapy and currently there is no established framework within the NHS for its diagnosis and management. This has led to considerable regional variation in the management of and in the treatments offered to people with varicose veins in the UK.

Terminology

Throughout the guideline we have used the internationally accepted vein terminology of great saphenous vein (GSV) for and small saphenous vein (SSV).

Two terms felt by the GDG to be of particular importance and thus worthy of highlighting were:

- **Symptomatic varicose veins** which were defined by the GDG as: those found in association with troublesome lower limb symptoms (typically pain, aching, discomfort, swelling, heaviness, and itching) that are thought to be due to the effects of superficial venous reflux and for which no other more likely cause is apparent.'

- **Vascular service** which was defined by the GDG as: 'a team of healthcare professionals who have the skills to undertake a full clinical and duplex Doppler ultrasound assessment and provide a full range of treatment.

1.1 Use of CEAP classification

Attempts to group like people together have been attempted with classifications such as the CEAP grading system. This provides a method of classifying varicose veins, providing information on the clinical severity, aetiology, anatomical location and pathophysiology of varicose veins. The clinical severity aspect of CEAP classification (for example, C1-C6) is used throughout the document, to match the outcomes used in the included randomised controlled trials. However, we recognise the limitations of using the clinical severity classification as an outcome measure, as it was not designed to be used as a measure of clinical change, or to provide referral criteria, and there is still uncertainty about how the stages interact with each other.

1.2 Aim of the guideline

This guideline aims to:

- identify which people should be referred and/or treated,
- identify which treatment is cost effective,
- provide information for people with varicose veins

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- the information for the public is written using suitable language for people without specialist medical knowledge.
- the NICE pathway links all recommendations and includes links to other relevant guidance

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is: to produce a clinical guideline on the management of varicose veins.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Alun Davies in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 4-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (appendix B).

Members were either required to withdraw completely, or for part of the discussion, if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

This guideline covers adults (18 and older) with primary or recurrent leg varicose veins. The particular needs of pregnant women are considered. Clinical issues covered by the guideline are:

- assessment for referral and treatment (including hand held Doppler, duplex scanning and clinical grading systems)
- conservative (including lifestyle advice and compression therapy) and interventional treatments (for example surgical treatments and thermal ablation treatments).
- information and support needs of patients and carers.

For further details please refer to the scope in appendix A and review questions in section 3.1.

2.5 What this guideline does not cover

The guideline does not cover children and young people (younger than 18) or those with venous malformation. It does not cover the management of:

- leg ulcers (other than the role of ablative truncal venous interventions)
- spider veins
- pelvic varicose veins, unless associated with primary or recurrent lower limb varicose veins
- varicose veins not located in the leg.

In addition the guideline does not review evidence for pharmacological, alternative or complementary treatments.

2.6 Relationships between the guideline and other NICE guidance

NICE Interventional Procedures to be incorporated into the guideline:

Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedure guidance 440 (2013).

Endovenous laser treatment of the long saphenous vein. NICE interventional procedure guidance 52 (2004). Available from www.nice.org.uk/guidance/IPG52

Transilluminated powered phlebectomy for varicose veins. NICE interventional procedure guidance 37 (2004). Available from www.nice.org.uk/guidance/IPG37

Radiofrequency ablation of varicose veins. NICE interventional procedure guidance 8 (2003). Available from www.nice.org.uk/guidance/IPG8

Related NICE Clinical Guidelines:

Obesity. NICE clinical guideline 43 (2006). Available from

Patient experience in adult NHS services. NICE clinical guideline 138 (2012). Available from http://guidance.nice.org.uk/CG138

Related NICE Public Health Guidance:

Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006). Available from

Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health guidance 1 (2006). Available from www.nice.org.uk/guidance/PH1

Promoting physical activity in the workplace. NICE public health guidance 13 (2008). Available from www.nice.org.uk/guidance/PH13

Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10

Physical activity and the environment. NICE public health guidance 8 (2008). Available from www.nice.org.uk/guidance/PH8

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009 [67]. Available from: www.nice.org.uk].

The evidence was reviewed following the steps shown schematically in in Figure 1.

Figure 1: Step by step process of the review of the evidence in the guideline

3.1 Developing the review questions and outcomes

For intervention reviews, review questions were developed in a framework encompassing definitions of the population, intervention, comparison and outcomes (PICO). For prognostic reviews, questions were developed with a framework of population, prognostic factor and outcomes. For diagnostic reviews, questions were developed with a framework of population, index tests, reference test and target condition. The scope of these questions was further defined by the 'protocol' for each question, where, alongside the question framework, search and analysis strategies and the inclusion and exclusion criteria were defined (appendix C). This was to guide the literature-searching process and to facilitate the development of recommendations by the guideline development group (GDG). Review question protocols were drafted by the NCGC technical team and refined and validated by the GDG. The question protocols were based on the key clinical areas identified in the scope (appendix A). A total of 15 review questions were identified. The finalised review questions are summarised in Table 1.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5	Observational and qualitative	What are the perceptions and expectations of people with varicose veins (e.g. natural history, treatment) and how can they be addressed?	Any outcomes that are identified by the participants in the studies Patient perceptions and expectations
6.1	Prognostic	In people with leg varicose veins at CEAP class C2 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C3, ii) C4, iii) C6? In people with leg varicose veins at CEAP class C3 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C4, ii) C6? In people with leg varicose veins at CEAP class C4 which signs, symptoms and/or patient characteristics are associated with disease progression to C6?	Progression of CEAP class
6.2	Prognostic	In people with leg varicose veins are there any factors (clinical signs and symptoms or patient reported outcomes) that would predict increased benefits or harms from varicose veins interventional treatments?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
7.1	Diagnostic	What is the diagnostic accuracy of hand held Doppler compared to duplex scanning when used in patients with varicose veins?	Sensitivity and specificity per tested vein
7.2	Intervention	Does the use of duplex ultrasound during assessment improve outcome after interventional treatment compared to no duplex scanning in people with leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
8.1	Intervention	What is the clinical and cost effectiveness of compression therapy compared with no treatment or lifestyle advice in people with leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
8.2	Intervention	What is the clinical and cost effectiveness of compression therapy compared with foam sclerotherapy in people with leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
8.2	Intervention	What is the clinical and cost effectiveness of compression therapy compared with stripping surgery in people with leg varicose veins	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux,

Chapter	Type of review	Review questions	Outcomes
			recurrence, return to work/activity.
8.2	Intervention	What is the clinical and cost effectiveness of compression therapy compared with endothermal ablation in people with leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
9.1	Intervention	What is the clinical and cost effectiveness of stripping surgery compared with foam sclerotherapy in people with truncal leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
9.2	Intervention	What is the clinical and cost effectiveness of stripping surgery compared with endothermal ablation in people with truncal leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
9.3	Intervention	What is the clinical and cost effectiveness of foam sclerotherapy compared with endothermal ablation in people with truncal leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
9.4	Intervention	What is the clinical and cost effectiveness of avulsion surgery compared with foam sclerotherapy in people with tributary leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
9.5	Intervention	What is the clinical and cost effectiveness of truncal vein treatment accompanied by tributary treatments compared with truncal vein treatment alone in people with leg varicose veins?	Quality of life, patient-assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.
10	Intervention	What is the clinical and cost effectiveness of interventional treatment followed by compression compared with interventional treatment alone in people with leg varicose veins, and, if so, what type of compression, pressure of compression and/or duration of compression is optimal?	Quality of life, patient-assessed assessed symptoms, physician-assessed outcomes, adverse events, complications of varicose veins, reflux, recurrence, return to work/activity.

3.1.1 Groups for special consideration

Two groups for special consideration were identified during the scoping stage;

- Pregnant women with varicose veins
- People with recurrent varicose veins

No specific review questions were developed for the populations of pregnant women with varicose veins and people with recurrent varicose veins, as both population groups were included in all the review questions. However because of the importance of these two groups, relevant findings that had been collected during the course of answering the guideline review questions were collated and discussed by the GDG.

People with recurrent varicose veins

The evidence for this population was discussed by the GDG but it was felt that separate recommendations were not required. Where the recommendation is relevant to people with recurrent varicose veins this has been made explicit in the wording of the recommendation.

Pregnant women with varicose veins

The evidence for this population group was summarised to inform specific and easily accessible recommendations. In some instances, searched evidence that had not previously been included in the review questions due to specific question exclusion criteria, but that had special relevance to this group. The information is presented in chapter 11.

3.2 Searching for evidence

3.2.1 Clinical literature search

The aim of the literature search was to systematically identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE Guidelines Manual [2009][67]. Databases were searched using medical subject headings and free-text terms. Foreign language studies were not reviewed and, where possible, searches were restricted to articles published in the English language. All searches were conducted in MEDLINE, Embase, and the Cochrane Library, and were updated for the final time on **17th October 2012**. No papers after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in appendix F.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

3.2.2 Health economic literature search

Systematic searches were undertaken to identify relevant health economic evidence within the published literature. The NHS Economic Evaluation Database (NHS EED), the Health Economic Evaluations Database (HEED) and Health Technology Assessment (HTA) database were searched using broad population terms and no date restrictions. A search was also run in MEDLINE and Embase using a specific economic filter with population terms. Where possible, searches were

restricted to articles published in the English language. Economics search strategies are included in appendix F. All searches were updated for the final time on **17th October 2012**. No papers published after this date were considered.

3.3 Evidence of effectiveness

The Research Fellows:

- Identified potentially relevant studies for each review question by reviewing titles and abstracts from the relevant search results. The full papers for these potentially relevant studies were then obtained.
- Reviewed the full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in appendix C).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual [National Institute for Health and Clinical Excellence (January 2009) - the guidelines manual. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk].
- Extracted key information about the study's methods and results, and transferred it into evidence tables (evidence tables are included in appendix G).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta analysed where appropriate, and reported in GRADE profiles
  - Observational studies: data presented as a range of values in GRADE profiles
  - Diagnostic studies: data presented as a range of values in adapted GRADE profiles
  - Prognostic studies: data from each study were summarised in a table and/or presented in a narrative
  - Qualitative studies: each study was summarised in a table where possible, but otherwise presented in a narrative.

Twenty per cent (20%) of each of the above stages of the reviewing process was quality assured by the second reviewer to eliminate any potential of reviewer bias or error

3.3.1 Inclusion/exclusion

See the review protocols in appendix C for full details.

Key population inclusion criteria were adults (18 years or over) with primary or recurrent varicose veins in their legs. Pregnant women were specifically included. Key population exclusion criteria were:

- Children and young people (younger than 18).
- People with venous malformations.
- People with varicose veins in places other than their legs.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question or there was a scarcity of evidence. In this case the authors of the selected abstracts were contacted for further information.

3.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each outcome in each review question. Cochrane Review Manager (RevMan5) software was used for this purpose.

Binary outcomes

Fixed-effects (Mantel-Haenszel) techniques, using an inverse variance method for pooling, were used to calculate risk ratios (relative risk) for the binary outcomes which were:

- the existence of patient-assessed symptoms
- patient satisfaction
- reflux or clinical recurrence
- adverse events
- development of complications of varicose veins

In addition to relative effects, absolute effect sizes were also calculated using the GRADEpro software, using the median event rate across the control arms of the individual studies in the meta analysis.

For variables where there were zero events in the comparator arm, Peto odds ratios, rather than risk ratios were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Continuous outcomes

The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes were:

- quality of life
- physician reported disease measures
- symptom scales (normally visual analogue scale (VAS))
- days to return to work/normal activity

Where the studies within a single meta-analysis had different continuous scales, standardised mean differences were used. This involved each study's mean difference measure being 'normalised' to the pooled intervention and comparator group standard deviation value. For example, if the mean difference was 18 and the pooled standard deviation value was 9, then the standardised mean difference would be 18/9 = 2.

The means and standard deviations of continuous outcomes were required for meta-analysis. In cases where standard deviations were not reported, the standard error of the mean difference was calculated from the mean difference values and either p-values or confidence intervals. Meta-analysis was then undertaken using the generic inverse variance method in Cochrane Review Manager (RevMan5.1) software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if p value was reported as "p ≤0.001", the calculations for standard error were based on a p value of 0.001. If p values or confidence intervals were not available then the methods described in section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied if possible. If these were not possible to apply, then meta-analysis was not carried out.

Statistical heterogeneity was assessed for both binary and continuous outcomes by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ and the I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable

heterogeneity). Where considerable heterogeneity was present, we carried out sensitivity analyses. Sensitivity analyses were carried out looking at the subgroups which were pre-specified by the GDG. If the heterogeneity still remained, a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect. For further details on assessing inconsistency see section 3.3.4.2.

Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers. Because of the nature of the evidence collected, with high variability of risk factors, outcomes and confounders considered, no quantitative data synthesis was carried out. Evidence was synthesised in narrative form.

Data synthesis for diagnostic test accuracy review

For diagnostic test accuracy studies, no meta-analysis of evidence was varied out. The following outcomes were reported for each test: sensitivity, specificity, positive predictive value, and negative predictive value. In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data to allow calculation of these accuracy measures. Summary receiver operative characteristic (ROC) curves were not generated as there were insufficient studies (<5) per test to allow a curve to be produced.

3.3.3 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 'summary of findings' were presented in a single GRADE table in this guideline. The 'Clinical/Economic Study Characteristics' section of the table includes details of the quality assessment while the 'Clinical /Economic Summary of Findings' section table includes pooled outcome data (where appropriate), an absolute measure of intervention effect, and the summary of quality of evidence for that outcome.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2 and each graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (section 3.3.4 - Grading of Evidence). The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (poor allocation concealment), performance and detection bias (a lack of blinding of the patient, health care professional and assessor) and attrition bias (not including drop-outs in the analysis).
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the

Quality element	Description
	clinically important threshold. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm).
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an over-estimate of the effect size for that outcome.

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.4 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW.
2. The rating was then downgraded for the specified criteria: Risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (that had not previously been downgraded) was upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have a “serious” or “very serious” risk of bias was rated at 1 or2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in the following sections 3.3.4.1 to 3.3.4.5.

3.3.4.1 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error (for example if a study were carried out several times there would be a consistently wrong answer, and the results would be inaccurate).

The risk of bias for a given study and outcome is associated with the risk of over-or underestimation of true effect. The risks of bias are listed in Table 4.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 4: Risk of bias in randomised trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number etc.)
Lack of blinding	Patients, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the research authors to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of un-validated patient-reported outcomes • Recruitment bias in cluster randomised trials

3.3.4.2 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. Some variation in effect sizes across studies will always be expected due to sampling error, but when estimates of the treatment effect across studies differ widely, this suggests true differences in underlying treatment effect. These differences may be due to differences in populations, settings, doses, or comparators.

Statistical heterogeneity was assessed for the overall meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$, or an I-squared inconsistency statistic of >50%, to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out sub-grouping of studies within the meta-analysis for the following pre-defined criteria:

- CEAP grade,
- Type of endovenous ablation (if relevant)

This was on the basis that any variations across studies in effect size might be at least partially due to variations in the sub-grouping factor. If such sub-grouping managed to reduce heterogeneity to acceptable levels within both of the derived sub-groups, then each of the derived sub-groups were adopted as separate outcomes, pending GDG approval (for example, instead of the single outcome of *reflux*, we would now have *reflux in studies where CEAP was predominantly C2-3* and *reflux in studies where CEAP was predominantly C4-6*).

Sub-grouping was always carried out for *CEAP grade* first. If this resolved heterogeneity then *type of endovenous ablation* was not used for sub-grouping. *Type of endovenous ablation* was only used for sub-grouping if *CEAP grade* was unable to resolve the inconsistency. Where subgroup analysis gave a plausible explanation of heterogeneity, the quality of evidence for each new sub-group outcome was not downgraded for inconsistency.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Such subgroup differences were interpreted with caution since they broke randomisation and were subject to uncontrolled confounding.

If sub-grouping was unable to resolve unacceptable statistical heterogeneity within each derived sub-group, then

- a random effects (DerSimonian and Laird) model was applied to the entire group of studies in the meta-analysis. A random-effects model allows for a distribution of populations, rather than assuming a single population. This leads to a widening of the confidence intervals around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across > 1 population.
- the quality of evidence for the outcome was downgraded by one level if the I squared value was between 50 and 74%, and by two levels if the I squared value was 75-100% (Table 3).

If, however, the GDG felt that the degree of heterogeneity was so large that meta-analysis was inappropriate, then the meta-analysis was not carried out.

3.3.4.3 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures in the included studies are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

For each study in the meta-analysis of an outcome, one aspect of indirectness led to single downgrade, whereas 2 or more aspects of indirectness led to a downgrade of 2 (Table 3). A weighted mean of downgrades across all the studies reporting that outcome in the meta-analysis was then carried out. The weighting was according to inverse variance, the same weighting criteria used for pooling the effect size.

3.3.4.4 Imprecision

The criteria applied for imprecision were based on the confidence intervals for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, existing either side of the line of no effect on a Forest plot. If either of the 95% confidence intervals of the overall estimate of effect crossed one of the MID lines, imprecision was regarded as serious, and a single downgrade for the outcome was carried out. If both MID lines were crossed by either or both of the confidence intervals then imprecision was regarded as very serious, and a downgrade of 2 was carried out (Table 3). This is illustrated in Figure 2.

The position of the MID lines is ideally determined by values as reported in the literature. “Anchor-based” methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or “anchoring” them to patient-centred measures of clinical effectiveness that could reasonably be regarded as gold standards with a high level of face validity. For example, the minimum amount of change in an outcome necessary to make a patient decide that they felt their quality of life had “significantly improved” might define the MID for that outcome. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For categorical variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual. Hence they are not amenable to patient-centred “anchor” methods, which rely on an individual’s perception of clinical importance.

In the absence of literature values, the alternative approach to deciding on MID levels is the “default” method, as follows:

- For categorical outcomes where the event is “positive” (for example, “patient satisfaction”) the risk ratio denoting a minimally important *benefit* for the intervention relative to the comparator (at a population level) is taken as 25% above no net effect: a risk ratio of 1.25.

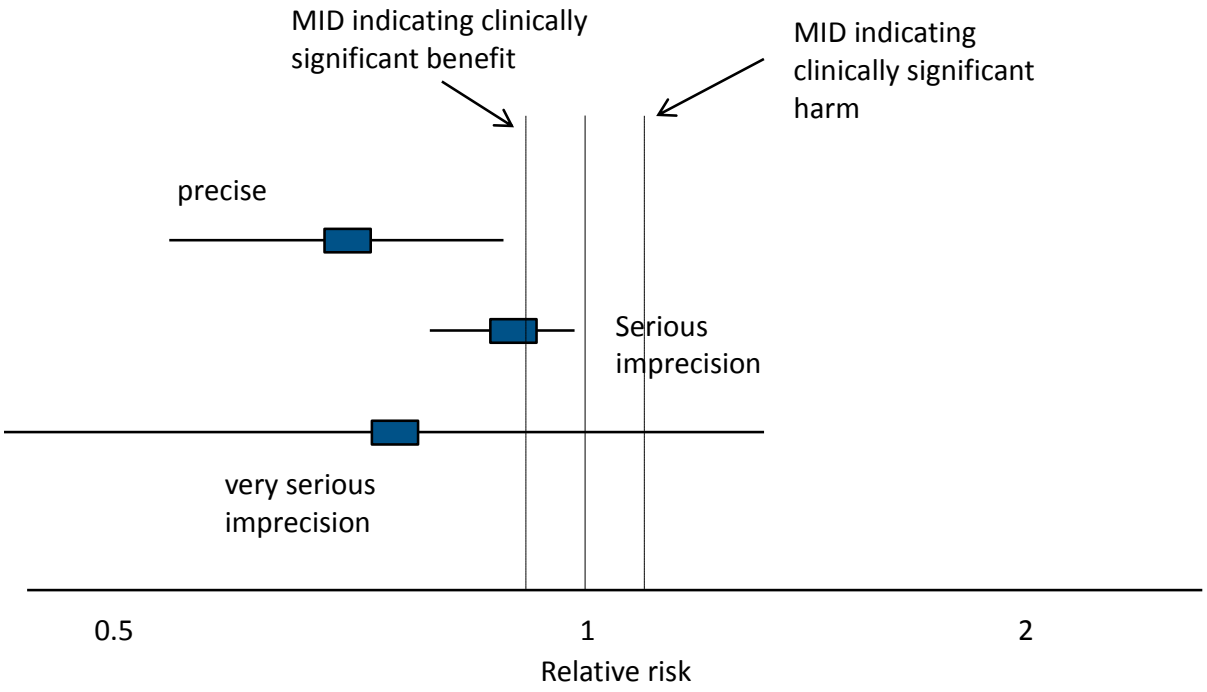
For such a "positive" outcome, the risk ratio denoting a minimally important *harm* for the intervention relative to the comparator will be the reciprocal of 1.25, and therefore 0.80.

- For categorical outcomes where the event is "negative" (for example "reflux recurrence") the risk ratio denoting a minimally important *benefit* for the intervention relative to the comparator (at a population level) is taken as 25% below no net effect: a risk ratio of 0.75. For such a "negative" outcome, the risk ratio denoting a minimally important *harm* for the intervention relative to the comparator will be the reciprocal of 0.75, and therefore 1.33.
- For continuous outcome variables the MID is taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. For example, if the median value of baseline standard deviations across all the meta-analysis studies is 10, then the MID will be ±5. In such a case, the MID denoting the minimum clinically significant benefit will be +5 for a positive" outcome (for example, a quality of life measure where a higher score denotes better health), or -5 for a "negative" outcome (for example, a VAS pain score). Clinically significant harms will be the converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.
- If standardised mean differences have been used, then the MID will be set at the absolute value of ± 0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the two groups, and are thus effectively expressed in units of "number of standard deviations". The 0.5 value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the GDG. If the GDG decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or binary outcomes were found in the literature, and so the default method was used.

Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of binary outcomes in a forest plot.



Source: Figure adapted from GRADEPro software.

The top result in Figure 2 was considered precise because the upper and lower 95% confidence intervals did not cross either MID. Conversely, the bottom two results on the diagram were considered imprecise because both of them crossed the MID and reduced our certainty of the results. Note that all three results would be pooled estimates, and results on the diagram were considered imprecise because both of them crossed the MID and reduced our certainty of the results. Note that all three results would be pooled estimates, and would not, in practice, be placed on the same forest plot.

3.3.4.5 Publication bias

Downgrading for publication bias would only be carried out if the GDG were aware that there was serious publication bias for that particular outcome. Such downgrading was not carried out for this guideline.

3.3.5 Appraising the quality of evidence for prognostic studies

The evidence for prognostic studies was evaluated according to the criteria given in Table 5.

Table 5: Description of quality elements for prospective studies

Quality element	Description of cases where the quality measure would be downgraded
Study design	If case control rather than prospective cohort
Patient recruitment	If potential for selection bias
Validity of risk factor measure(s)	If non-validated and no reasonable face validity
Validity of outcome measure	If non-validated and no reasonable face validity
Blinding	if assessors of outcome not blinded to risk factor measurement (or vice versa)
Adequate follow-up (or retrospective) duration	If follow-up/retrospective period inadequate to allow events to occur, or retrospective period so short that causality is in doubt because the outcome may have preceded the risk factor
Confounder consideration	If there is a lack of consideration of all reasonable confounders in a multivariable analysis
Attrition	If attrition is too high and there is no attempt to adjust for this.
Directness	If the population, risk factors or outcome differ from that in the review question.

Because prognostic reviews were not usually based on multiple outcomes per study, quality rating was assigned by study. However if there was more than one outcome involved in a study, then the quality rating of the evidence statements for each outcome was adjusted accordingly. For example, if one outcome was based on an invalidated measurement method, but another outcome in the same study wasn't, the latter outcome would be graded one grade higher than the other.

Quality rating started at HIGH for prospective studies, and each major limitation (section 3.3.3) brought the rating down by one level to a minimum grade of LOW, as explained for interventional studies.

3.3.6 Appraising the quality of evidence for diagnostic studies

Evidence for diagnostic data was evaluated by study, using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists. Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (Table 6):

- Patient selection
- Index test

- Reference standard
- Flow and timing

Table 6: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias; (high/low/unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

(a) Source: University of Bristol –QUADAS-2 website (http://www.bris.ac.uk/quadas/quadas-2)

Quality rating started at HIGH, and each major limitation brought the rating down by one level to a minimum grade of LOW, as explained for interventional studies.

3.3.7 Clinical evidence statements

Clinical evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty/uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the two tested treatments).
- A description of the overall quality of evidence (GRADE overall quality).

3.4 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- undertook a systematic review of the economic literature
- undertook new cost-effectiveness analysis in a priority area.

3.4.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual.[67]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual[67]) and the health economics review protocol in appendix C.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual.[67] It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 7 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[73]

Table 7: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective

Item	Description
	QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

**Limitations and applicability were assessed using the economic evaluation checklist from appendix of The Guidelines Manual.*[67]

Where economic studies compare multiple strategies, results are presented in the economic evidence profiles for the pair-wise comparison specified in the review question, irrespective of whether or not that comparison was 'appropriate' within the analysis being reviewed. A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in a priority area. The priority area for new health economic analysis was agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

To parameterise treatment effects in the model, a network meta-analysis (NMA) was carried out. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomization of RCTs included in the reviews of direct comparisons. The aim of the NMA was to include all relevant evidence in order to calculate treatment-specific hazard ratios for use in the model. We used statistical models for fixed and random effects that allowed inclusion of multi arm trials and accounted for the correlation between arms in the trials with any number of trial arms. The code for the NMA was adapted from the NICE Technical Support Unit website, and run in WinBUGS 14. Heterogeneity and inconsistency were investigated using the methods described in Dias et al (2012)[25] and Dias et al (2012a).[26] Further details about the NMA can be found in appendix L and the NMA code in appendix M.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See appendix L for details of the health economic analysis undertaken for the guideline.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[66,67]

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[66]

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H
- summary of clinical and economic evidence and quality (as presented in chapters 5-11)
- forest plots (appendix I)
- a description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (appendix L)

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation. The wording of recommendations was agreed by the GDG and focused on the following factors:

- on the actions health professionals need to take
- include what readers need to know
- reflect the strength of the recommendation (for example the word "offer" was used for strong recommendations and "consider" for weak recommendations)
- emphasise the involvement of the patient (and/or their carers if needed) in decisions on treatment and care
- follow NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Section for each chapter.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

3.5.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Key priorities for implementation

From the full set of recommendations, the GDG selected 5 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual.[71] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

- Refer people to a vascular service if they have:
  - symptomatic primary or recurrent varicose veins **or**
  - lower-limb skin changes (such as pigmentation or eczema) thought to be caused by chronic venous insufficiency.

- Refer people to a vascular service if they have:
  - a venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks) **or**
  - a healed venous leg ulcer.

- Consider using duplex ultrasound to confirm the diagnosis and to plan treatment for people with suspected primary or recurrent varicose veins.

- Offer interventional treatment to people with confirmed varicose veins and truncal reflux as follows:
  - Offer endothermal ablation.
  - If endothermal ablation is not suitable or is declined, offer ultrasound-guided foam sclerotherapy.
  - If ultrasound-guided foam sclerotherapy is unsuitable or is declined, offer surgery.

  If incompetent varicose tributaries are to be treated, consider treating them at the same time.

- Offer compression hosiery only if interventional treatment is not suitable or is declined.

4.2 Full list of recommendations

Information for people with varicose veins

1. Give people who present with varicose veins information that includes:
   - an explanation of what varicose veins are
   - possible causes of varicose veins
   - the likelihood of progression and possible complications, including deep vein thrombosis, skin changes, leg ulcers, bleeding and thrombophlebitis. Address any misconceptions the person may have about the risks of developing complications
   - treatment options, including symptom relief, compression and a brief overview of interventional treatments

- lifestyle changes that may help, for example:
  i. weight loss (for guidance on weight management, see Obesity [NICE clinical guideline 43])
  ii. light to moderate physical activity (for example, walking or swimming)
  iii. avoiding factors that are known to make their symptoms worse if possible (for example, some people find prolonged standing or hot baths make their symptoms worse)
- when and where to seek further medical help.

2. When discussing treatment for varicose veins at the vascular service, tell the person:
   - what treatment options are available
   - the expected outcomes and possible adverse events of each treatment option
   - that new varicose veins may develop after treatment
   - that they may need more than 1 session of treatment
   - that the chance of recurrence after treatment for recurrent varicose veins is higher than for primary varicose veins.
3. Refer people with bleeding varicose veins to be seen by a vascular service immediately or within 24 hours.
4. Refer people with a recent history of minor bleeding from varicose veins to be seen by a vascular service within 2 weeks.
5. Refer people to a vascular service if they have:
   - symptomatic primary or recurrent varicose veins **or**
   - lower-limb skin changes (such as pigmentation or eczema) thought to be caused by chronic venous insufficiency.
6. Refer people with superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected superficial venous incompetence to a vascular service.
7. Refer people to a vascular service if they have:
   - a venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks) **or**
   - a healed venous leg ulcer.
8. Consider using duplex ultrasound to confirm the diagnosis and to plan treatment for people with suspected primary or recurrent varicose veins.
9. Offer interventional treatment to people with confirmed varicose veins and truncal reflux as follows:
   - Offer endothermal ablation.
   - If endothermal ablation is not suitable or is declined, offer ultrasound-guided foam sclerotherapy[a].
   - If ultrasound-guided foam sclerotherapy is unsuitable or is declined, offer surgery.

   If incompetent varicose tributaries are to be treated, consider treating them at the same time.
10. Offer compression hosiery only if interventional treatment is not suitable or is declined.

[a]Recommendation linked to Ultrasound-guided foam sclerotherapy for varicose veins (IPG440).

11. Do not offer compression bandaging or hosiery for more than 7 days after completion of interventional treatment for varicose veins.
12. Give pregnant women presenting with varicose veins information on the effect of pregnancy on varicose veins.
13. Do not carry out interventional treatment for varicose veins during pregnancy other than in exceptional circumstances.
14. Consider compression hosiery for symptom relief of leg swelling associated with varicose veins during pregnancy.

4.3 Key research recommendations

- In people with varicose veins at CEAP (Clinical, etiological, anatomical and pathophysiological) stage C2 or C3, what are the factors that influence progression of the disease to CEAP stages C5 or C6?
- Does the early treatment of superficial venous reflux together with compression therapy improve wound healing and result in greater cost effectiveness compared with compression therapy alone in patients with chronic venous ulceration?
- What is the clinical and cost effectiveness of completing concurrent phlebectomies for varicose tributaries during truncal endothermal ablation for varicose veins compared with
  - truncal endothermal ablation without concurrent phlebectomies?
  - truncal endothermal ablation with subsequent phlebectomies if needed 6-12 weeks later?
- What is the clinical and cost effectiveness of compression hosiery versus no compression for the management of symptomatic varicose veins?
- What is the clinical and cost effectiveness of compression hosiery after interventional treatment for varicose veins compared with no compression hosiery? If there is a benefit, how long should compression hosiery be worn for?

5 Patient perceptions and expectations

Patient expectations and perceptions concerning varicose veins may be derived from many sources. The most common sources include GP clinics and hospitals, conversations with family and friends, direct experience of others with the condition, and information on the internet and in the mass media. Some of these sources are misleading, unreliable and can be conflicting. This results in confusion and may lead to some people with varicose veins becoming more anxious. The information given can lead to unrealistic expectations about 1) the likely progression of varicose veins, and 2) the outcomes of any treatment. Such unrealistic expectations may have a negative effect on a person's quality of life.

To minimise misconceptions throughout all stages of care it is crucial to ensure that people with varicose veins are fully informed about their condition. People need information of the range of evidence-based treatments available, and their possible risks, to enable them to make properly informed choices.

It is hard for people with varicose veins to identify good quality information on the diagnosis and management of varicose veins. This emphasises the urgent need to provide such guidance, together with the most effective means of promoting and providing this information.

5.1 Review question: What are the perceptions and expectations of people with varicose veins (e.g. natural history, treatment) and how can they be addressed?

For full details see review protocol in appendix C.

Table 8: Characteristics of review question

Setting	Primary and secondary care
Population	Adults with leg varicose veins.
Intervention	NA
Comparison	NA
Evaluation	Narrative summary of findings on patient perceptions and expectations related to the assessment, treatment, treatment success/failure, retreatment, adverse events and disease progression of varicose veins. Studies suggesting how such expectations can be addressed were also evaluated.

5.2 Clinical evidence

This review has been separated into three sections:

- Expectations and perceptions about varicose veins
- Managing expectations and perceptions
- Communicating information

The first section encompasses the first part of the review question (*What are the perceptions and expectations of people with varicose veins?*), and the latter two sections encompasses the second part of the review question (*How can they be addressed?*).

5.2.1 Expectations and perceptions about varicose veins

Summary of included studies

Six studies were identified that were relevant to the review question concerning the expectations and perceptions of people with varicose veins. Five of the studies recruited people who had been referred for treatment to a vascular clinic [15,22,27,74,95]. One was a qualitative study [74] , whilst the other 5 were questionnaire surveys [15,22,27,95,107]. The qualitative study[74] was graded as 'moderate' quality as it used the appropriate methodological approach for evaluating patient perceptions, but did not describe the timing of the data collection clearly. Four of the surveys [22,27,95,107] were graded as 'very low', as they had used closed questions within a quantitative format, and most failed to report their questionnaires adequately. One survey [15] was graded as 'low', as although it did not apply appropriate qualitative techniques it did use open questions and the questionnaire was well-reported. The studies are summarised in Table 9.

See also the study selection flow chart in appendix D, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 9: Summary of studies analysing patient perceptions and expectations

STUDY	Population/setting	Methodology	Quality
Palfreyman 2004[74]	n=16. Patients referred for varicose vein treatment. Those with complications such as ulcers or bleeding were excluded. Setting: a large NHS secondary care trust in Sheffield.	Purposive sampling used to ensure gender and age range. 22 patients were approached but 6 were unable to participate due to other commitments. Qualitative – semi-structured interviews conducted. Unclear when carried out: "conducted between 5 and 14 days after surgical out-patient clinic prior to referral to a vascular surgeon by a GP".	Unclear how much information the patients would have received at the prior surgical out-patients clinic, which could have affected results. Trustworthiness of collected data was made more likely through the use of established methods (framework analysis), the on-going reflection and discussion amongst researchers, and the use of feedback of interpretations to patients both during and after interviews. Graded as moderate quality.
Darvall 2009[22]	n=282. Patients about to undergo foam sclerotherapy for symptomatic varicose veins. Setting: Large NHS secondary care trust	Consecutive patients given Likert style questionnaire one week before treatment and 6 months after treatment Results presented quantitatively, as proportions.	Prone to bias through the scope of answers being decided by the pre-defined and closed questions. Questions described but no actual questionnaire provided. Good response rate of 80% indicates the results are probably representative. Graded as very low quality.
Campbell 2006[15]	n=190. Patients referred to a vascular unit with uncomplicated varicose veins. Setting: unclear but likely to be a vascular unit in an NHS secondary care trust.	No information given on selection of patients. Questionnaire containing a mixture of open and closed questions, given prior to first attendance at vascular clinic.	62% completion rate. Open questions were provided concerning worries and fears about varicose veins, reducing the risk of bias due to leading questions. However some bias was present through these questions asking about concerns or worries rather than a more neutral concept such as "feelings about the future". The whole questionnaire was contained in the appendix of the paper. Graded as low quality.
Dillon 2005[27]	n=82. Patients with	Questionnaire administered	This is part of a before and after study

STUDY	Population/setting	Methodology	Quality
	newly diagnosed varicose veins referred for surgery. Setting: randomly selected vascular clinics in Republic of Ireland.	at randomly selected clinics to all patients referred with varicose veins. Questionnaire contained closed questions. The time at which the questionnaire was administered is unclear, but likely to have been before the vascular consultation. Results presented quantitatively, as proportions.	evaluating the impact of information giving to people prior to surgery (see evidence table in appendix G). In this section we describe the results of the questionnaire prior to the intervention. 100% completion rate of the initial questionnaire. Prone to bias through the scope of answers being decided by the pre-defined and closed questions. Questions described but no actual questionnaire provided. Graded as very low quality.
Shepherd 2010[95]	n=111. Patients referred to a vascular surgeon with symptomatic varicose veins. Setting: vascular clinic in an NHS secondary care trust.	Consecutive patients referred to a vascular surgeon were invited to take part. Questionnaire contained closed questions. The time at which the questionnaire was administered is unclear, but likely to have been before the vascular consultation as stated that no information was given to the patient prior to the questionnaire. Results presented quantitatively, as proportions.	75% response rate. Prone to bias through the scope of answers being decided by the pre-defined and closed questions. Whole questionnaire contained in the appendix of the paper. Graded as very low quality.
Zubilewicz 2009[107]	n=156. Patients (women only) with chronic venous disease (CVD), with no previous treatment. Setting: Poland but no other details provided.	No information on patient selection. Multiple choice questionnaire study, but little information given on the questions used.	Prone to bias through the scope of answers being decided by the pre-defined and closed questions. Questions described but no actual questionnaire provided. Graded as very low quality.

5.2.1.1 Narrative summary

As only Darvall 2009 reassessed people's expectations and perceptions post treatment these results do not inform us about the accuracy of their perceptions and expectations.

Palfreyman 2004

This moderate quality qualitative study of 16 varicose vein patients elicited both positive and negative expectations about varicose veins treatment and disease processes.

Positive expectations were expressed about the anticipated treatment effects on current symptoms. As one patient stated: "…more than anything is that it won't be as it is now, so that the pain factor, the heaviness, everything that goes with it hopefully will have gone…" There were also positive expectations of the effect of treatment on prognosis, with the expectation that surgery would

prevent future deterioration of symptoms and limit the extent of varicose veins. Patients either had the expectation of no possibility of recurrence, or that even a short symptom free period would be worth it. Even those with previous surgery expected that their surgery this time would work better, and that even a short symptom free period would be worth it.

Negative expectations were held of the disease prognosis if treatment was not given. An important motivation for treatment was that deep vein thrombosis (DVT) and ulceration could occur later because of their varicose veins. A particular concern was that varicose veins could exacerbate the risks of flying on development of a DVT. Negative expectations about the adverse events of surgery were also stated. Fear of surgery was common: "….I'm in the middle now. I'm frightened of having them done and I'm frightened of having them..."

Darvall 2009

This questionnaire survey aimed to assess the expectations of treatment effects in 282 patients prior to treatment. This study involved 373 legs, and expectations of symptoms were presented in terms of numbers of legs, presumably because differing levels of severity across legs in a single patient might lead to differing levels of expectations about symptom improvement. Most data were presented in low resolution graphs, and so the tabular data below are approximate.

A significant improvement in overall symptoms as a result of treatment was expected by patients in 33% of legs, and a moderate improvement was expected in 67%. The detailed expectations data for individual symptoms are given below in Table 10.

Table 10: Percentage of patients' legs [n=373] associated with expectations of significant or moderate improvement in symptoms

Symptom	Expectation of significant improvement	Expectation of moderate (but not significant) improvement
Pain	37%	63%
Itch	32%	68%
Tingling	24%	76%
Cramp	30%	70%
Restless legs	29%	71%
Swelling	37%	63%
Heaviness	37%	63%

There were also positive expectations of how treatment would affect the appearance of the legs, and lifestyle factors such as being able to wear certain clothes. These results, presented as percentages of patients, are summarised in Table 11.

Table 11: Percentage of patients [n=282] expecting significant or moderate improvement in lifestyle. Figures are based on a low resolution graph and so are approximate.

Aspect of lifestyle	Expectation of significant improvement	Expectation of moderate (but not significant) improvement
Appearance of the legs	60%	30%
Choice of clothes that can be worn	30%	40%
Performance at work	27%	40%
Enjoyment of leisure activities	27%	40%
Relationships	10%	15%

A second questionnaire was given 6 months after surgical treatment to ascertain any mismatch between expectations and what actually happened. Table 12 summarises the percentages of legs (for symptoms) or patients (for other factors) that did not have their expectations met.

Table 12: Percentages where pre-operative expectations were not met 6 months post-operatively

	Factor	Legs [n=365] or patients [n=281] where expectations were not met
Symptoms	Pain	20%
	Itch	21%
	Tingling	18%
	Cramp	23%
	Restless legs	22%
	Swelling	27%
	Heaviness	18%
Other factors	Appearance of the legs	12%
	Choice of clothes that can be worn	25%
	Performance at work	25%
	Relationships	14%
	Enjoyment of leisure activities	30%

Campbell 2006

This questionnaire survey of 190 patients aimed to assess negative expectations about the anticipated course of the disease in the absence of treatment, using closed questions directing the respondent to further open comments. Overall 79% of the patients reported at least one concern or worry about their varicose veins. Table 13 summarises the fears that patients had about the future.

Table 13: Fears associated with the anticipated course of the disease [n=190].

Fear	Patients with the fear
Future thrombosis	31%
Future trauma or bleeding	16%
Future ulcers	15%
Future circulatory disease	12%
Future phlebitis	4%
General concerns about the future	30%

Dillon 2005

This questionnaire study of 82 patients set out to evaluate patient expectations about the perceived risks of varicose veins, and the expectations of surgery. Significant personal anxiety caused by having varicose veins was reported by 41% of respondents. Table 14 summarises the perceptions of varicose vein risks and Table 15 summarises the expectations of surgery.

Table 14: Perceptions of varicose veins risks [n=82]

Perceived risk	Patients with this belief
High risk of developing ulcers	56%
High risk of developing DVT	50%

Perceived risk	Patients with this belief
High risk of bleeding from minor injuries	32%
High risk of developing gangrene	33%

Table 15: Expectations of surgery [n=82, unless stated]

Surgical expectation	Patients with this belief
Surgery will improve appearance	80%
Surgery will improve pain	77%
Surgery will improve itch	76%
Surgery will improve heaviness	77%
Surgery will improve flares[a]	67%
Recovery after surgery will take <2 weeks [n=72]	79%
Return to work after surgery will take 1 month or more [n=72]	21%

(a) No definition of 'flares' was given in the paper.

Shepherd 2010

This questionnaire survey of 111 patients presented much of its data in low resolution graphs, and so the data given below are approximate. The study showed that 36/99 (35%) of respondents were "extremely concerned" about recurrence, and 16/101 (16%) were "extremely concerned" about discomfort after treatment.

With regard to treatment options available:

- 86% were aware of surgery as an option
- 32% were aware of laser ablation
- 22%were aware of sclerotherapy
- 18% were aware of radiofrequency ablation.
- 10% were unaware of any treatments.

24/103 (23%) expressed a preference for endovenous treatments (i.e. endothermal or foam sclerotherapy) over surgery. Of the endovenous treatments, laser was the most popular (the first choice of 11%). 72% patients (74/103) stated that they didn't know enough to express a treatment preference.

Zubilewicz 2009

This questionnaire study of 156 Polish women evaluated the perceptions about modifiable risk factors for chronic venous disease. The results are summarised in Table 16.

Table 16: Perceived modifiable risk factors for chronic venous disease [n=156].

Perceived risk factors	% of participants holding the belief
Overweight/obesity	85%
High-heeled footwear	73%
Standing position at work	71%
Sitting position at work	61%
Pregnancy	58%
Crossing legs	51%

Perceived risk factors	% of participants holding the belief
Long journeys by car or plane	40%
Oral contraceptives	30%
Use of depilatory wax	17%
Under-floor heating	11%
Physical activity	20%

In terms of the expectations of the effects of chronic venous disease, >50% of those aged <65 years assessed chronic venous disease as a severe disorder that lessened quality of life. Approximately 70% of women more than 65 years old considered chronic venous disease as especially serious. Overall, 33.3% believed that chronic venous disease was a risk factor for ulceration, but about 70% of women under 30 years regarded chronic venous disease as a primarily cosmetic problem.

5.2.1.2 Synthesis of evidence

Expectations of varicose veins natural history

Expectations generally reflected an exaggerated sense of risk from varicose veins. DVT and ulceration were deemed probable events by patients in the qualitative study[74], and over half of respondents in a questionnaire study[27] thought ulcers were likely. In the same study[27], one third of patients also felt gangrene was a very high risk. However a higher quality qualitative study [15] revealed that only 15% feared future ulcers.

Expectations of effects of treatment

Expectations were generally that treatment would be highly effective in terms of improving symptoms. The qualitative study[74] suggested that patients felt treatment would eradicate symptoms. In one qualitative study[27] about 75% of patients expected improvements in symptoms, and in another [22] all patients expected at least some improvement. Interestingly, approximately 20% of patients in that study[22] had their high expectations unmet.

Expectations of improvements in lifestyle [22] were more modest, with around 70% expecting improvements in the choice of clothes, enjoyment of leisure activities and performance at work, and 25% expecting an improvement in relationships. Nevertheless, the proportion with unmet expectations was similar to that for symptoms (approximately 25%).

Expectations of adverse events

Fear of surgery was expressed in the qualitative study[74]. Another study showed that 16% were extremely concerned about discomfort after treatment.[95] 21% of participants in another study [27] thought that it would take more than a month to return to work.

Expectations of treatments available

In one study, most patients were unaware of the existence of endovenous treatments.[95] Most patients admitted their knowledge was insufficient to make a choice.

Perceptions of risk factors

In one study[107] there was evidence of inaccurate identification of risk factors, with 17% of patients believing the use of depilatory waxes were a risk factor. 11% also thought under-floor heating increased risk. Most patients knew that being overweight was a risk factor, but only 58% were aware that pregnancy also heightened the probability of developing varicose veins.

5.2.2 Managing expectations and perceptions

Two papers[15,74] made suggestions as to how patient expectations could be managed. These papers have been included in section 5.2.2, and details of their methodology are outlined in Table 17.

Palfreyman 2004[74] suggested that information given to patients should be based on consideration of their expectations. This view was echoed by Campbell 2006[15] who also explained that reassuring patients with expectations of poor prognosis might prevent many electing for intervention.

5.2.3 Communicating information

Two quantitative studies[11,27] were identified that answered the review question concerning approaches to manage patient expectations. These studies assessed the suitability of two specific strategies: the informed consent process,[27] or an information booklet[11]. One of these studies[27] was the same study as described in the previous section. Quality was graded as 'very low' in studies, [11,27] as limitations included the lack of a comparison group and high attrition rates. Table 17 summarises these studies.

Table 17: Studies evaluating strategies to address patient expectations

STUDY	Population/setting	Methodology	Quality
Dillon 2005[27]	n=82. Patients with newly diagnosed varicose veins referred for surgery. Setting: randomly selected vascular clinics in Republic of Ireland.	Evaluated the effects of the standard informed consent process on expectations. The informed consent process involved an in-depth discussion of the nature and consequences of surgery. The same questionnaire assessing expectations was used before the informed consent process, and 2 weeks after, but before any surgery had been given.	This was a 'before and after' study, without the use of a control group, and was therefore prone to threats to internal validity. One such threat arose because the questionnaire was administered differently at the pre- and post-tests, carried out in the conventional way in the pre-test, but by telephone in the post-test (for all but one of the respondents). This could have influenced any changes after the intervention. Finally, there was attrition of 15 patients in terms of completion of the follow-up questionnaire, which could also have biased results. Graded as 'very low' quality.
Bobridge 2011[11]	n=26. Patients with chronic venous insufficiency (CVI) at grades CEAP stage C3-C6, diagnosed with duplex, recruited from a vascular clinic. Setting: Australian General Hospital.	Assessed the impact of an information booklet, which had been developed from the best-available evidence. It contained lay term information on the pathophysiology of CVI and the importance of skin care, leg elevation, exercise, diet and compression garments. The booklet was provided by a vascular nurse specialist who explained its contents. The patients were expected to read the booklet and undertake the booklet's recommended activities at home over the next 6 months. Assessment	Assessment was carried out with the use of validated questionnaires such as the Health Education Impact Questionnaire, and the CVI questionnaire, but the presented outcomes (such as "feeling nervous and tense") appeared to be only sub-units of these. Absolute pre- and post-test values of these measures were not given and the magnitude of any changes was not presented. This was a 'before and after' study without a comparison group, with attrition of 6 patients. Graded as 'very low' quality.

STUDY	Population/setting	Methodology	Quality
		of perceptions of health occurred at baseline and 1 and 6 months after the booklet had been given.	

5.2.3.1 Narrative summary

Informed consent process

Dillon 2005[27] evaluated whether the normal informed consent process occurring during patient consultation was capable of changing unrealistic patient expectations. Table 18 summarises the changes in expectation occurring after the informed consent process. These changes were described as non-significant.

Table 18: Changes in patient expectations occurring after the informed consent process

Expectation	Proportion with expectation pre-informed consent [n=82]	Proportion with expectation 2 weeks post informed consent (but before surgery) [n=67]
Surgery will improve appearance	80%	90%
Surgery will improve pain	77%	84%
Surgery will improve itch	76%	80%
Surgery will improve heaviness	77%	86%
Surgery will improve flares	67%	31%
It will take a month or more to return to work	21%	27%
Varicose veins carry a high risk of developing ulcers	56%	60%
Varicose veins carry a high risk of developing DVT	50%	49%
Varicose veins carry a high risk of bleeding from minor injuries	32% (n=26)	67% (n=45)
Varicose veins carry a high risk of developing gangrene	33%	28%

Information booklets

Bobridge 2011[11] investigated the effects of giving information booklets to patients. Many effects were reported, but only three were relevant to patient perceptions. At 6 months post-administration there were "significant improvements" in each of the following chronic venous insufficiency -related perceptions:

- worrying about chronic venous insufficiency
- feeling a sense of hopelessness about chronic venous insufficiency
- feeling nervous and tense.

5.3 Economic evidence

Published literature

No cost effectiveness evidence was identified for this question.

5.4 Evidence statements

5.4.1 Clinical

Expectations or perceptions about varicose veins disease processes and treatment

Expectations of varicose veins natural history

- Three studies comprising 288 participants suggested that an exaggerated sense of the risk of varicose veins may exist in patients [LOW QUALITY].

Expectations of effects of treatment on symptoms

- Three studies comprising 380 participants suggested that most patients expect symptoms to be improved by treatment [VERY LOW QUALITY].

Expectations of effects of treatment on improvements in lifestyle

- One study comprising 282 participants suggested that about 70% of patients expect lifestyle to be improved by treatment [VERY LOW QUALITY].

Expectations of adverse events

- Three studies comprising 209 participants suggested that patients are fearful of surgery and expect recovery to be long [VERY LOW QUALITY].

Expectations of treatments available

- One study comprising 111 participants showed that most patients had insufficient knowledge about available treatments to be able to make an informed choice [VERY LOW QUALITY].

Perceptions of risk factors

- One study comprising 156 participants showed that patient perception of risk factors were often inaccurate [VERY LOW QUALITY].

How such expectations or perceptions can be addressed

Informed consent process

- One study comprising 82 participants showed that the informed consent process was ineffective in changing patient expectations [VERY LOW QUALITY].

Information booklet

- One study comprising 26 participants showed that provision of an information booklet containing the best available evidence could help to improve varicose vein-related perceptions such as anxiety and a sense of hopelessness [VERY LOW QUALITY].

5.4.2 Economic

No cost effectiveness evidence was identified for this question.

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2 5.5 Recommendations and link to evidence

3 5.5.1 Patient information at first consultation

Recommendations	**1. Give people who present with varicose veins information that includes:** • **an explanation of what varicose veins are** • **possible causes of varicose veins** • **the likelihood of progression and possible complications, including deep vein thrombosis, skin changes, leg ulcers, bleeding and thrombophlebitis. Address any misconceptions the person may have about the risks of developing complications** • **treatment options, including symptom relief, compression and a brief overview of interventional treatments** • **lifestyle changes that may help, for example:** i. **weight loss (for guidance on weight management, see Obesity [NICE clinical guideline 43])** ii. **light to moderate physical activity (for example, walking or swimming)** iii. **avoiding factors that are known to make their symptoms worse if possible (for example, some people find prolonged standing or hot baths make their symptoms worse)** • **when and where to seek further medical help.**
Relative values of different outcomes	The outcomes used in this review were any reported in the papers. The GDG considered any reported perceptions and expectations as equally important.
Trade off between clinical benefits and harms	The evidence reviewed suggested that people had pessimistic perceptions of the likelihood of developing complications such as ulcers if their disease progressed, high expectations of treatment success, and a poor understanding of the lifestyle risk factors for the disease. There was a scarcity of evidence on how information should be given to people with varicose veins wanting information. There are few, if any, harms from exploring perceptions and expectations at the initial consultation and by providing accurate information for people with varicose veins. There was some concern within the GDG that raising issues that had not been considered by the person with varicose veins (e.g. gangrene) may increase their anxiety. It was felt, therefore, that although misconceptions should be explored it was not necessary to introduce new factors that may cause anxiety and that information should be tailored to the person and their needs. Palfreyman 2004[74] and Campbell 2006[15] suggested that information given to people should be based on consideration of their expectations.
Economic considerations	It was expected that the impact of providing patient information on time and resource use would be minimal, and would likely be offset by an improvement in quality of life. Reassuring people with expectations of poor prognosis might prevent many electing for intervention. [15]
Quality of evidence	Eight studies were included in this section (1 qualitative, 7 quantitative surveys). The quality of evidence was moderate for the qualitative data (1 study). Quality was graded as low or very low for the quantitative surveys (7 studies). Survey methods are not optimal for exploring expectations and perceptions, and questionnaires may use closed and potentially leading questions.

Other considerations	Alongside the evidence review, the recommendation was based on the list of topics that the patient member of the GDG provided for the guideline development group about what they would like to know about varicose veins. A key message from the evidence was that people with varicose veins had pessimistic perceptions of the likelihood of developing complications such as ulcers if their disease progressed, high expectations of treatment success, and a poor understanding of the lifestyle risk factors for the disease. There is little reliable information available in the literature on the proportion of people with varicose veins who progress to venous ulceration. One study reported that 28.6% of those who had visible varicose veins without oedema or other complications progressed to more serious venous disease after 6.6 years.[80] However there was no information about the numbers progressing to ulceration. Other data on the lifetime prevalence of varicose veins estimates that approximately 3-6% of people who have varicose veins in their lifetime will develop venous ulcers.[68] , The GDG considered that education of healthcare professionals was an important issue. The GDG felt that a brief overview of the different treatment options was appropriate at this stage to ensure patients were aware of the options, but that a detailed description of the precise process or the risks and benefits of the options was not necessary. The evidence reviewed in chapter 6 identified a high body mass index as a factor that both increased the risk of progression to more serious varicose veins and was also a factor predicting worse outcome after treatment compared with a normal body mass index. The GDG felt that light to moderate exercise (for example, walking or swimming) may help but that strenuous exercise may aggravate varicose veins. It is important to note that aggravating factors are individual to the person with varicose veins. The experience of the primary care members of the GDG was that people with varicose veins had often worked out what the factors were that exacerbated their symptoms (e.g. hot baths, prolonged standing) and they should be advised to avoid these factors where possible. The patient should be informed that if they experience hard painful veins, skin changes, a break in the skin on their leg lasting for longer than 2 weeks or any bleeding from the varicose veins they should come back to seek further medical help. The GDG noted there was information about varicose veins was available on the internet. This could be an unreliable source of information that does not provide comprehensive information on the range of management options available and/or their adverse effects. It may be beneficial for the healthcare professional to recommend specific reliable resources if desired by the person with varicose veins. The recommendation has been developed to be specific to the information needs of people with varicose veins. The NICE patient experience guideline provides further, more generic, recommendations to improve the experiences of those using the health service and should be consulted as required.

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Recommendations	**2. When discussing treatment for varicose veins at the vascular service, tell the person:** • **what treatment options are available** • **the expected outcomes and possible adverse events of each treatment option** • **that new varicose veins may develop after treatment** • **that they may need more than 1 session of treatment** • **that the chance of recurrence after treatment for recurrent varicose veins is higher than for primary varicose veins.**

5.5.2 Patient information prior to treatment

Relative values of different outcomes	The outcomes considered for this review were people's perceptions and expectations and these were all considered equally important by the GDG.
Trade off between clinical benefits and harms	There are few, if any, harms from providing accurate, relevant information when discussing treatment options and exploring expectations from surgery. The evidence found suggested that with varicose veins had overly optimistic expectations of treatment success. However there were also exaggerated perceptions of adverse effects, such as prolonged periods of recovery post-surgery. People were often unaware of the possible treatments available.
Economic considerations	It was expected that the impact of providing patient information on time and resource use would be minimal, and would likely be offset by an improvement in quality of life. Reassuring patients with expectations of poor prognosis might prevent many electing for intervention.[15]
Quality of evidence	Eight studies were included in this section (1 qualitative, 7 quantitative surveys). The quality of evidence was moderate for the qualitative data. Quality was graded as low or very low for the survey collected data. Survey methods are not optimal for exploring expectations and perceptions, and questionnaires may use closed and potentially leading questions.
Other considerations	The GDG felt that it was important that patients should have information about the risks and benefits of the treatment options so that they are fully informed before they make a decision about whether to undergo treatment. The chance that further varicose veins may develop after treatment (which were new varicose veins rather than treatment failure) and the possibility that treatment may require more than one session were felt to be important to ensure that patients had a realistic expectation of treatment success before treatment. A review of the data from the trials of interventional procedures indicates that the rate of clinical recurrence of varicose veins at 3 years is likely to be between 10-30%. One of the aspects which prevents being able to provide clear figures on retreatment rates is the fact that many of the treatments are relatively new and the long term rates have not yet been published. There is evidence to suggest that people with recurrent varicose veins have a poorer outcome following treatment than those being treated for primary varicose veins (section 6.2). The GDG noted that this was consistent with clinical experience where they found that recurrent disease was associated with a worse outcome after treatment than for primary varicose veins. The recommendation has been developed to be specific to the information needs of people with varicose veins. The NICE patient experience guideline provides further, more generic, recommendations to improve the experiences of those using the health service and should be consulted as required.

6 Referral to a vascular service

The key decision to be made in primary care is whether or not a patient should be referred to a vascular service. The main reasons for referring a person with varicose veins are to alleviate their symptoms and to prevent the progression of disease. A substantial variation exists in who is referred and how patients are treated, with some individuals being offered only lifestyle advice, whilst others are referred to a vascular service for interventional treatment.

Two review questions were therefore developed to identify evidence for the indications for referral. The first was a prognostic review, aimed at identifying the patient characteristics, symptoms and signs (that can be assessed prior to referral to a vascular service) that are associated with a higher likelihood of disease progression (section 6.1). The rationale for this question was that patients more likely to progress to the more severe stages of the disease should be prioritised for referral for early treatment.

The second review question was also a prognostic review, aimed at identifying the patient characteristics, symptoms and signs (that can be assessed prior to referral to a vascular service) that are associated with better or worse outcomes after interventional treatments (section 6.2). The rationale for this question was that patients who are more likely to respond well to treatment should also be prioritised for referral for treatment.

As the initial presentation is generally in a non-specialist setting, we have focussed on prognostic factors that might be determined without the need for specialist investigations, and so measures such as vein diameter were not included.

The GDG were aware of the limitations of using the CEAP classification for identifying progression (section 1.1.), but as there is no other defined progression scale, and it has been used by much of the literature, it was used as the definition of progression.

We recognised that certain patients might not have predictive markers for progression or a good response to treatment, yet would still benefit greatly from treatment due to impaired quality of life. However, the lack of an absolute quality of life threshold for “appropriate referral” would make any evidence-based decision on quality of life recruitment thresholds very difficult.

6.1 Review question:

a) In people with leg varicose veins at CEAP class C2 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C3, ii) C4, iii) C6

b) In people with leg varicose veins at CEAP class C3 which signs, symptoms and/or patient characteristics are associated with disease progression to i) C4, ii) C6?

c) In people with leg varicose veins at CEAP class C4 which signs, symptoms and/or patient characteristics are associated with disease progression to C6?

For full details see review protocol in appendix C.

Table 19: PICO characteristics of review question

Population	Adults with leg varicose veins at CEAP stage C2 OR C3 OR C4 [as in parts a), b) and c) of the clinical question]
Prognostic factors	Clinical signs that can be assessed prior to referral to a vascular service: • Location/extent of varicose veins • Any other aspects of physical examination Clinical symptoms that can be assessed prior to referral to a vascular service: • Severity of pain • Severity of other varicose veins symptoms Patient characteristics that can be assessed prior to referral to a vascular service: • Age • Body mass index (BMI) • Comorbidities • Pregnancy/no of previous pregnancies • Severity of pain • Severity of other varicose veins symptoms • Past history of deep vein thrombosis (DVT) • Recurrent varicose veins
Outcomes/end-points	Progression to the CEAP class endpoints defined by parts a), b) or c) of the clinical question
Study design	Pooled individual patient data, cohort and case control studies.

6.1.1 Clinical evidence

Summary of included studies

Four eligible studies were included in the review. One [76] was graded as "low" quality, and 3[12,90,93] were graded as "very low" quality. Only three studies carried out multivariable analysis[76,90,93], and in

one of these the model included variables that compromised the analysis [90]. Details of these studies, and other reasons for their quality grading, are given in Table 20.

Due to the small amount of evidence identified, the authors of all relevant abstracts were contacted and asked to provide detailed information on the methodology and results of their studies. One author [76] responded to our request and the information sent was used despite lacking some details. Information was not received from any of the other authors despite reminders being sent, and so these abstracts were excluded (appendix J).

See also the study selection flow chart in appendix D, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 20: Summary of studies included in the review.

STUDY	Population description (sample size)	Tested risk factors	Progression*** definition	Methodology	Comments	Quality*
Pannier 2011[76]	Participants sampled from Bonn, Germany, who were C2 at baseline (n=290)	Gender, height, blood pressure, BMI, subjective symptoms, work stress / strenuousness, activity, smoking, alcohol, quality of life.	From C2 to C3-6	Prospective cohort study, evaluating the associations between the risk factor levels and the risk of progression to C3-6.	Published as an abstract, with additional information gathered from the authors. It was unclear if participants received treatment during the 6 year follow-up.	Low[a]
Robertson 2009[90]	Patients scanned in a vascular laboratory in Scotland, with a CEAP range from C2-6. (n=240)	Age, gender, smoking, physical exercise, daily activity, past medical history.	From C2-4 to development of ulceration (C5 or C6)	Case control study, with cases being C5/6 and controls being C2-4. Potential confounders were either matched between groups, or adjusted for in the analysis.	Some risk factor variables, such as "physical exercise aged 35-45" or "daily activity aged 35-45", would have preceded ulceration in most, but not all cases, as some patients may have remained in these age categories at the time of analysis, based on the means and variance of age given, this would threaten the prognostic value of these variables. Other risk factors included in the multivariable analysis were cross-sectional, and therefore not prognostic Their inclusion in the analysis meant the prognostic value of the multivariable model was adversely affected.	Very Low[b]
Scott 1995[93]	Patients with varicose veins without ulceration	Age, gender, past medical history.	From "varicose veins" [CEAP stage C2-C3] to ulceration [CEAP stage C5-C6]	Case control study, with cases described as chronic venous insufficiency (CVI) grades II and III, and controls described	It is not clear that all the CVI grade II and III patients had ulcers, but there is an indication that is the case in the paper.	Very Low[c]

STUDY	Population description (sample size)	Tested risk factors	Progression*** definition	Methodology	Comments	Quality*
	and those with ulcers all recruited from the same vascular clinic. (n=222)			as having varicose veins without "CVI". Potential confounders were not matched between groups, but were adjusted for in the multivariable analysis.		
Boccalon 1997[12]	Patients with CVI of legs, previously treated with 2 months of daily 1g microflavanoid fractions (n=666)	Age, gender, secondary aetiology**	No skin changes (C2-3) to skin changes (C4-6)	Case-control study, comparing the frequency of risk factors in the 3 groups (no skin changes, skin changes without ulceration, skin changes with ulceration).	Most analysed factors considered were cross-sectional and so not prognostic.	Very Low[d]

** Overall, one downgrade led to a quality grading of "moderate", two downgrades led to "low" and more than two led to "very low".*

***In this review, primary aetiology refers to cases due to venous valve defects, whereas secondary aetiology refers to cases secondary to obstruction by a previous DVT*

**** "progression" has also been used to relate to case control methodology studies, as although case control studies do not strictly measure progression, their implication is that the state of the cases represents a progression of the state of the controls.*

(a) Downgraded for no report of blinding of assessor and incomplete information given by abstract authors.

(b) Downgraded for indirectness and for the use of case control methodology instead of prospective, lack of blinding of assessors, unreported attrition rates, possible selection bias and the inclusion of inappropriate variables in the multivariable analysis.

(c) Downgraded for indirectness and for the use of case control studies instead of prospective, and unclear reporting of outcomes.

(d) Downgraded for indirectness and for the use of case control studies instead of prospective, unclear measurement validity, lack of blinding of assessors, unclear levels of attrition, and a lack of consideration of confounders in the analysis.

6.1.1.1 Narrative summary

6.1.1.1.1 Prospective studies

Pannier 2011[76]

Out of 290 people with C2 at baseline (who also attended 6.6 year follow-up), 83 (28.6%) went on to develop C3-6 6.6 years later. A multivariate analysis showed that there was an increased risk of progression from C2 to C3-6 over 6.6 years with greater baseline age, increased baseline BMI , and a subjective "swelling feeling" at baseline. The other factors had too great an uncertainty in their direction of effect to be sure of their impact on disease progression (Table 21).

Table 21: Multivariable results from Pannier for the relative risk of progression from C2 to C3-6 over 6.6 years

Risk factor	RR (95% CI) of the progression from C2 to C3-6
Being female (vs. male)	1.31 (0.89,1.94)
Age (continuous; per year increment increase in age)	1.02 (1.01, 1.04)
Pre-hypertension (vs. normal blood pressure)	2.07 (0.77, 5.58)
Stage 1 hypertension (vs. normal blood pressure)	1.41 (0.46, 4.32)
Stage 2 hypertension (vs. normal blood pressure)	1.26 (0.52, 3.01)
BMI 25 to <30 (vs. <25)	2.56 (1.54, 4.28)
BMI 30 to <40 (vs. <25)	2.86 (1.65, 4.94)
BMI >40 (vs. <25)	3.47 (1.01, 11.93)
Leg heaviness lasting 4 weeks (vs. none)	1.07 (0.64, 1.79)
Feeling of leg tension lasting 4 weeks (vs. none)	1.25 (0.71, 2.20)
Swelling feeling in leg lasting 4 weeks (vs. none)	1.68 (1.01, 2.81)
Pain during prolonged walking lasting 4 weeks (vs. none)	0.96 (0.53, 1.72)
Leg itching lasting 4 weeks (vs. none)	0.89 (0.46, 1.70)

6.1.1.1.2 Case control studies

Robertson 2009[90]

Univariable analysis evaluated several factors (Table 22) that might have a prognostic effect on the risk of developing ulceration. All odds ratios (ORs) were adjusted for age and sex, as cases were older [64.1 vs. 59.9; p=0.01] and more often male [55% vs. 43%; p=0.07]. It was unclear whether most risk factors increased or decreased risk, with the exception of smoking, where reduced ulceration was associated with lower levels of smoking.

Table 22: Univariable results from Robertson 2009 relating to lifestyle

Risk factor	OR (95% CI) for ulceration[a]	Comparator
Smoking (pack years)	1.08 (0.9, 1.29)	Increment increase in smoking pack years
Light physical exercise at ages 35-45	0.86(0.37, 2.01)	compared to no physical exercise at ages 35-45
Moderate physical exercise at ages 35-45	0.76(0.34, 1.68)	
Strenuous physical exercise at ages 35-	1.29(0.48, 3.49)	

Risk factor	OR (95% CI) for ulceration[a]	Comparator
45		
Typical daily activity at ages 35-45 – walking	1.09(0.49, 2.41)	compared to typical daily activity of sitting at ages 35-45
Typical daily activity at ages 35-45 – light loads	0.79(0.31, 2.03)	
Typical daily activity at ages 35-45 – heavy work	0.86(0.35, 2.10	

*(a) This is the OR (95% CI) for ulceration for every increment increase of the risk factor (continuous variables) **or** for the existence of the risk factor compared to the reference category (categorical variables).*

Medical history was also compared across cases and controls (Table 23). It is not clear if these factors had preceded ulceration, though this is likely in many cases.

Table 23: Univariable results from Robertson 2009 relating to past medical history

Risk factor	% with risk factor in cases	% with risk factor in controls	Effect size OR (95% CI)
History of phlebitis	44/120 (37%)	34/120 (28%)	1.46(0.85, 2.52)[a]
History of leg fracture	22/120 (18%)	13/120 (11%)	1.85(0.88, 3.87)[a]
History of arthritis	48/120 (40%)	42/120 (35%)	1.24(0.73, 2.09)[a]
Ever smoked	77/120 (63.6%)	55/120 (45.6%)	2.12(1.26, 3.55)[a]

(a) ORs/mean differences and 95% CIs were not stated in the original paper, but have been calculated by members of the NCGC technical team

A multivariable analysis was carried out to attempt to evaluate the independent effects of each risk factor. No potentially prognostic factors remained in the model after stepwise logistic regression. It should be noted that the model included cross-sectional factors such as reflux and BMI, and so the prognostic validity of the model may have been reduced.

Scott 1995[93]

Scott 1995 considered many cross-sectional factors that could not have had any prognostic value (such as current BMI), so these have not been presented in this review. The potentially prognostic unadjusted effects of factors on ulceration are provided in Table 24.

Table 24: Univariate risk factors for ulceration (adjusted for age and sex).

Risk factor	Cases (ulceration)	Controls ("varicose veins")	Effect size (ORs/mean differences and 95% CIs)
History of heart disease	21/93 (22.6%)	6/129 (4.6%)	OR: 5.98 (2.31, 15.50)[a]
History of diabetes mellitus	21/93 (22.6%)	3/129 (2.3%)	OR: 12.25 (3.53, 42.50)[a]
History of hypertension	46/93 (49.5%)	21/129 (16.3%)	OR: 5.03 (2.71, 9.35)[a]
History of kidney disease	4/93 (4.4%)	3/129 (2.3%)	OR: 1.89 (0.41, 8.64)[a]
History of arthritis	18/93 (19.7%)	18/129 (13.9%)	OR: 1.48 (0.72, 3.03)[a]
History of leg injury[b]	51/93 (54.8%)	23/129 (17.8%)	OR: 5.60 (3.05, 10.28)[a]
History of phlebitis/clot	42/93 (45.6%)	31/129 (24.2%)	OR: 2.60 (1.47, 4.62)[a]

Risk factor	Cases (ulceration)	Controls ("varicose veins")	Effect size (ORs/mean differences and 95% CIs)
History of oral contraceptive use[c]	5/93 (5.1%)	27/129 (20.7%)	OR: 0.21 (0.08, 0.58)[a]
Years smoked [mean(sd)]	17 (1.7)	8.8(1.0)	MD: 8.20 (7.81, 8.59)[a]

(a) ORs/mean differences and 95% CIs were not stated in the original paper, but have been calculated by authors of the review
(b) History of leg injury defined as: serious leg injury such as a broken leg, burn, stab or gunshot wound, or a crush injury
(c) It is unclear whether the % given in the paper was out of all subjects or just females. However, the tabular presentation of results in the paper suggests the % represented all patients. Hence the surprising result for oral contraceptive results may simply be an artefact of a greater proportion of women in the control group (this would automatically lead to a greater % using contraceptives). If the calculation is redone using the same numerators, but the number of women as denominator, then the significant effect disappears [OR: 0.43 (0.15, 1.21)], which supports this assertion.

A multivariable analysis was carried out to assess the independent effects of each risk factor. The multivariable model did include two variables that were cross-sectional (BMI and no health insurance), which may have reduced the prognostic validity of the model, but male gender and a history of leg injury or diabetes mellitus were shown to be independent prognostic factors for ulceration (Table 25).

Table 25: Multivariable analysis carried out by Scott 1995

Risk factor	OR for ulceration
age	1.07/year (1.04-1.1)
male gender	8 (3.5-18.3)
BMI	1.07/kg/m2(1.01-1.13)
no health insurance	3.2 (1.3-7.7)
history of leg injury[a]	4.7 (2.1-10.5)
Diabetes mellitus	4.3 (0.99-18.7)

(a) History of leg injury defined as: serious leg injury such as a broken leg, burn, stab or gunshot wound, or a crush injury

Boccalon 1997[12]

Gender

The most severe form of skin changes (ulceration and "pre-ulceration changes") occurred in 12/70 men compared to 49/596 women. Although not presented in the paper, our calculations showed that men had 2.31 (1.16, 4.59) times the odds of having the most severe skin changes compared to the women. However when comparing the proportions of men with skin changes of any level (37/70) and women with skin changes of any level (318/596), our calculations showed men had no greater odds [OR: 0.98 (0.60, 1.61)].

Age

The mean age appeared to increase with greater severity (Table 26).

Table 26: Association of age with severity

Risk factor	Group 1 (<C4)	Group 2 (skin changes not including pre-ulceration or ulceration)	Group 3 (more severe skin changes including pre-ulceration or ulceration)
Age (mean/sd)	45(14)	53(15)	65(13)

Other factors

Other factors were considered but they were cross-sectional and so do not indicate prognosis for progression.

6.1.2 Economic evidence

No cost effectiveness evidence was identified for this question.

6.1.3 Evidence statements

6.1.3.1 Clinical

Risk factors for progression from CEAP 2 to CEAP 3-6

Being female

- 1 prospective study comprising 290 participants suggested that being female at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than being male but the direction of this effect was uncertain [LOW QUALITY].

Age

1 prospective study comprising 290 participants suggested that greater age at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up [LOW QUALITY].

Hypertension

- 1 prospective study comprising 290 participants suggested that having **pre-hypertension** at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than having normal blood pressure, but the direction of this effect was uncertain [LOW QUALITY].
- 1 prospective study comprising 290 participants suggested that having **stage 1 hypertension** at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than having normal blood pressure, but the direction of this effect was uncertain [LOW QUALITY].
- 1 prospective study comprising 290 participants suggested that having **stage 2 hypertension** at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than having normal blood pressure, but the direction of this effect was uncertain [LOW QUALITY].

Body Mass Index (BMI)

- 1 prospective study comprising 290 participants suggested that having **BMI 25 - <30** at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than having BMI <25 [LOW QUALITY].
- 1 prospective study comprising 290 participants suggested that having **BMI 30 - <40** at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than having BMI <25 [LOW QUALITY].
- 1 prospective study comprising 290 participants suggested that having **BMI ≥40** at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than having BMI <25 [LOW QUALITY].

Subjective feeling of leg heaviness

- 1 prospective study comprising 290 participants suggested that a subjective feeling of heaviness lasting 4 weeks at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than no subjective feeling of heaviness, but the direction of this effect was uncertain [LOW QUALITY].

Subjective feeling of leg tension

- 1 prospective study comprising 290 participants suggested that a subjective feeling of leg tension lasting 4 weeks at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than no subjective feeling of leg tension, but the direction of this effect was uncertain [LOW QUALITY].

Subjective feeling of swelling in the leg

- 1 prospective study comprising 290 participants suggested that a subjective feeling of swelling in the leg lasting 4 weeks at baseline is associated with the **more** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than no subjective feeling of swelling in the leg [LOW QUALITY].

Pain during prolonged walking

- 1 prospective study comprising 290 participants suggested that pain during prolonged walking lasting 4 weeks at baseline is associated with **less** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than no pain during prolonged walking, but the direction of this effect was highly uncertain [LOW QUALITY].

Itching

- 1 prospective study comprising 290 participants suggested that itching in the past 4 weeks at baseline is associated with **less** likely progression from CEAP 2 to CEAP 3-6 at 6.6 year follow-up than no itching, but the direction of this effect was uncertain [LOW QUALITY].

Risk factors for ulceration

Male gender

- 2 case control studies comprising 888 participants suggested that male gender is associated with a **more** likely development of ulceration. This appeared to be a clinically important effect [VERY LOW QUALITY].

Past history of diabetes

- 1 case control study comprising 222 participants suggested that a history of diabetes is associated with the **more** likely development of ulceration, but the direction of this effect was slightly uncertain [VERY LOW QUALITY].

Past history of leg injury

- 1 case control study comprising 222 participants suggested that a history of leg injury is associated with the **more** likely development of ulceration. This was a clinically important effect [VERY LOW QUALITY].

6.1.3.2 Economic

No cost effectiveness evidence was identified for this question.

6.2 Review question: In people with leg varicose veins are there any factors (clinical signs and symptoms or patient reported outcomes) that would predict increased benefits or harms from varicose veins interventional treatments?

For full details see review protocol in appendix C.

Table 27: PICO characteristics of review question

Population	Adults with leg varicose veins
Prognostic Factors	Clinical signs and symptoms that can be assessed prior to referral to a vascular service: • Any aspects of physical examination (CEAP stage) • Patient-assessed symptoms (including pain, discomfort, cosmetic concerns/cosmesis, swelling (oedema), aching, heaviness.) Patient characteristics that can be assessed prior to referral to a vascular service: • Age • Body mass index (BMI) • Comorbidities • Parity • Recurrent varicose veins • Medical history (including family history) Patient reported outcomes that can be assessed prior to referral to a vascular service: • health-related quality of life, using generic (e.g. Medical Outcomes Study Short Form 36, EQ-5D) • disease-specific validated tools (e.g. Chronic Venous Insufficiency Questionnaire, Aberdeen Varicose Vein Symptom Severity Score).
Outcomes	• Patient-reported outcome:- ○ Health-related quality of life, using generic and disease specific validated tools. ○ Patient-assessed symptoms • Physician-reported outcomes (CEAP) • Presence of reflux • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work/normal activities
Study design	Studies must carry out a multivariable analysis, considering feasible confounders. Only prospective studies will be included.

6.2.1 Clinical evidence

Summary of included studies

Seven prospective studies were included in the review.[32,35,37,43,55,62,102] Two were graded as moderate quality[32,62], two as low quality [37,55] and three as very low quality. [35,43,102] Details of these studies, and reasons for their quality grading, are given in Table 28. See also the study selection flow chart in appendix D, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 28: Summary of studies included in the review.

STUDY	Population description (n)	Treatments	Tested risk factors	Outcomes measuring treatment success or failure	Methodology	Comments	Quality*
Fischer 2006[32]	Patients of unknown chronic venous insufficiency (CVI) severity (n=1261 patients /1638 legs)	Sapheno-femoral junction (SFJ) ligation and stripping of the Great saphenous vein (GSV)	BMI, age, gender, diabetes, leg side affected (right or left), prior parity, interim pregnancy.	Reflux: Sapheno-femoral reflux recurrence at a mean of 6.6 years	Prospective observational study. Multivariable analysis used to evaluate independent modifiers of treatment success.	Used a sophisticated imputation model to cater for missing baseline data. Adjusted for varying follow-up times. “Interim pregnancy” included as a factor but since this is not a pre-treatment factor it has not been reported in this review. Further information about varicose veins during pregnancy can be found in Chapter 11	Moderate
Gibson 2007A[35]	CEAP stage C2-6 patients (n=187patients / 210 legs)	Endothermal ablation (laser)	Gender, leg side affected (right or left), pre-op presence of ulcer, pre-op presence of stasis, pre-op presence of pain, and age.	Incidence of deep vein thrombosis (DVT) at 2-4 days. Incidence of recanalisation at 2-11 months	Prospective observational study. Multivariable analysis used to evaluate independent modifiers of treatment success and adverse events.	This paper included some risk factors that could not be assessed by a GP, such as duplex-assessed anatomic pattern of the small saphenous vein. These have not been included in this review.	Very Low[a]

STUDY	Population description (n)	Treatments	Tested risk factors	Outcomes measuring treatment success or failure	Methodology	Comments	Quality*
Gonzalez-Zeh 2008[37]	CEAP stage C2-6 patients (n=98)	Foam sclerotherapy and endothermal ablation (laser).	pre-op Venous Clinical Severity Score (VCSS), age, pre-op clinical CEAP class	Reflux: Existence of reflux at one year	Non-randomised trial with main aim of comparing 2 treatments, but additional multivariable analysis to investigate factors influencing post-op reflux for each treatment separately.	The reference category for the CEAP categorical variable is unclear.	Low[b]
Islamoglu 2011[43]	CEAP stage C2-6 patients (n=372)	Foam sclerotherapy (with crossectomy) and stripping surgery.	Unilateral/bilateral[f] symptoms pre-op CEAP, familial predisposition, gender, DVT, age, smoking, alcohol, diabetes, hypertension.	Patient reported outcomes: symptom recurrence Physician reported outcomes:, post-op CEAP, post-op PI at a mean of 10.2(5.1) months	Main aim was the comparison of foam and stripping, but in the absence of a differential treatment effect most of the multivariable analysis focussed on the non-treatment predictors of treatment success/failure.	Poor reporting of the multivariable analysis results.	Very low[c]
MacKenzie 2002[55]	CEAP stage C2-6 patients (n=203)	Greater saphenous vein surgery , small saphenous vein surgery or sub-fascial endoscopic perforator surgery (SEPS)	Age, gender, pre-operative Aberdeen varicose veins symptom severity score (high = worse), CEAP grade, primary/recurrent , history of DVT	Patient reported outcomes: Post-op AVVQ at 6 months and 2 years follow-up.	Prospective study of consecutive and unselected patients. A multivariable linear regression was used.	Well conducted study. Skewed AVVQ data was transformed before the analysis.	Low[d]
Myers 2007[62]	CEAP stage C2-6 patients	Ultrasound guided sclerotherapy	Age, gender, leg side, CEAP grade.	Physician reported outcomes: status of veins (absent,	Prospective observational study. Multivariable Cox regression analysis used to	Up to 4 treatment sessions were given, until full occlusion was noted. This was a time to	Moderate

STUDY	Population description (n)	Treatments	Tested risk factors	Outcomes measuring treatment success or failure	Methodology	Comments	Quality*
	(n=489 patients/ 807 veins)	(mainly foam but some liquid)		occluded, patent or refluxing) checked at intervals of up to 2 years	evaluate independent modifiers of treatment success.	event study, and time to reflux recurrence was the duration between the first treatment session (out of the 1-4) achieving full success and the first follow-up when reflux was noted.	
Thomasset 2010[102]	CEAP stage C2-5 patients (mostly C3-4)(n=116/126 veins)	Foam sclerotherapy	Gender, previous surgery pre-procedure, CEAP grade, compliance with post treatment compression, age.	Physician reported outcomes: Successful outcome (complete occlusion of the target vein on duplex analysis on follow-up.) Adverse events and complications from varicose veins: superficial thrombophlebitis, pain, skin staining, DVT, allergy and skin blistering	Prospective cohort study. Univariate analyses performed for the risk factors, but only one was significant for each outcome, making a multivariable analysis an unnecessary next step.	Poorly reported study.	Very Low[e]

** Overall, one downgrade led to a quality grading of "moderate", two downgrades led to "low" and more than two led to "very low". All studies were downgraded for a lack of assessor blinding. For five studies, further downgrades were as below:*

(a) downgraded for unclear follow-up duration, unacceptable levels of attrition, and unclear measurement validity of a principal risk factor
(b) downgraded for an unclearly reported multivariable analysis
(c) downgraded for unclear attrition and an unclearly reported multivariable analysis
(d) downgraded for unclear attrition
(e) downgraded for unclear attrition and no confounders analysed
(f) unilateral symptoms affect one leg, bilateral symptoms affect both legs

6.2.1.1 Narrative summary

6.2.1.1.1 Predictors of outcome after surgery

Fischer 2006

Fischer 2006[32] evaluated the baseline patient-related factors influencing reflux recurrence at a mean of 6.6 years after sapheno-femoral ligation and stripping surgery. Multivariable analysis showed that BMI>29 and prior parity were both associated with an increased odds of reflux recurrence. Table 29 shows the results of the multivariable logistic regression for relevant patient-related factors.

Table 29: Factors associated with reflux recurrence at 6.6 years (Fischer 2006)

Variable	OR (95% CIs)
BMI >29 at baseline (compared to <29)	1.65(1.12,2.43)
Prior parity (compared to none)	2.69(1.45,4.97)

MacKenzie 2002

MacKenzie 2002[55] evaluated the baseline patient-related factors influencing quality of life (AVVQ) after surgery, using a multivariable linear regression analysis at 6 months and 2 years.

<u>6 months multivariable analysis</u>

A higher baseline AVVQ, recurrent disease at baseline and CEAP stage C4 disease at baseline each independently predicted deterioration in AVVQ at 6 months after surgery. This model explained 60% of the total variance in AVVQ at 6 months (Table 30).

Table 30: Factors influencing AVVQ at 6 months (MacKenzie 2002)

Factor	Effect size[a]	SE	P value
square root of baseline AVVQ	0.57	0.07	<0.001
recurrent (versus first time)	0.45	0.17	0.009
CEAP C4 (versus CEAP C2-3)[b]	0.39	0.17	0.026

(a) The effect size, if positive, represents the multiple by which the AVVQ score would increase per one unit change in the factor (if continuous) or the multiple by which the AVVQ score would increase for the index category compared to the referent (if categorical). If negative, the parameter represents the multiple by which the AVSSS score would decrease.

(b) The paper was unclear about the reference grades, but one of the paper co-authors thinks that C2-3 was a likely comparator

<u>2 years multivariable analysis</u>

A higher baseline AVVQ and CEAP 5 disease at baseline each independently predicted deterioration in AVVQ at 2 years after surgery. In contrast, previous greater saphenous vein (GSV) surgery predicted a lower AVVQ. This model explained 47% of the total variance in AVVQ at 2 years (Table 31).

Table 31: Factors influencing AVVQ at 2 years (MacKenzie 2002)

Factor	Effect size[a]	SE	P value
square root of baseline AVVQ	0.47	0.08	<0.001

Factor	Effect size[a]	SE	P value
previous GSV surgery (versus not)	-0.73	0.31	0.02
CEAP 5 (versus C2-3)[b]	0.62	0.28	0.030

(a) The effect size, if positive, represents the multiple by which the AVVQ score would increase per one unit change in the factor (if continuous) or the multiple by which the AVVQ score would increase for the index category compared to the referent (if categorical). If negative, the parameter represents the multiple by which the AVVQ score would decrease.

(b) paper was unclear about the reference grades, but one of the paper co-authors thinks that C2-3 was a likely comparator

6.2.1.1.2 Predictors of outcome after endothermal laser ablation (EVLA)

Gibson 2007

Gibson 2007[35] examined baseline patient-related factors influencing the odds of DVT occurrence 2-4 days after laser endothermal ablation, using a multivariable logistic regression analysis. No risk factors assessable by a non-specialist had an association with DVT incidence at p<0.1 on univariate testing (Table 32). Hence no multivariable analysis was required.

Table 32: Univariate patient-related risk factors for DVT (Gibson 2007)

Risk factor for DVT (reference given in brackets)	OR (95% CI) for DVT at 2-4 days
Right side (compared to left)	0.64(0.20, 2.09)
Stasis (compared to no stasis)	0.46 (0.1, 2.16)
Age (per 10 year increment)	0.99 (0.62,1.57)
Gender	0/28 DVTs in men, 12/182 DVTs in women, p=0.4*
Pre-op ulcer	0/11 DVTs in those with ulcers, 12/199 DVTs in those with no ulcers, p=0.5*
Pain	0/13 DVTs in those with pain, 12/197 DVTs in those with no pain, p=0.5*
ulcer, stasis or pain	0/11 DVTs in those with ulcers, stasis or pain 12/199 DVTs in those with no ulcers, stasis or pain , p=0.5*

**Odds ratios not calculable due to zero values*

A multivariable logistic regression analysis using the same potential risk factors was also carried out to evaluate their effects on the odds of recanalisation at 2-11 months. None of the risk factors were reported to have a significant relationship with recanalization, and none of the univariate results were presented.

Gonzalez-Zeh 2008

Gonzalez-Zeh 2008[37] evaluated the baseline patient-related factors influencing reflux at one year for 45 patients after laser endothermal ablation. Multivariable logistic regression analysis (Table 33) was used to assess risk factors for reflux. It showed that no non-specialist-assessable factors predicted reflux without high levels of uncertainty about the direction of effect.

Table 33: Factors assessed for effects on the odds of reflux at one year (Gonzalez-Zeh 2008)

Variable	OR (95% CI)
clinical groups CEAP stage C4-6 (compared to CEAP stage C2-3[a])	2.87(0.33, 24.77)
Venous Clinical Severity Score (VCSS)b	0.31(0.03, 3.12)
Age[b]	0.94(0.79, 1.09)

(a) Unclearly reported
(b) Although not stated, likely that the ORs for reflux for the continuous variables (age, VCSS) are per increment increase in those variables

6.2.1.1.3 Predictors of outcome after foam sclerotherapy

Myers 2007

Myers 2007[62] assessed the baseline patient-related factors influencing the time to recurrence of reflux in all saphenous veins, after foam sclerotherapy. Table 34 summarises the results of the multivariable Cox-regression analysis, with a higher hazard ratio (HR) indicating the relative likelihood of reflux at any point in time compared to the reference category. Younger age was associated with earlier time to reflux. For other factors the direction of effect was very uncertain.

Table 34: Factors influencing time to recurrence (Myers 2007)

Variable (and reference)	Level	n	HR (95% CI)
Age (compared to 50-59)	<40	93	2.16 (1.27,3.66)
	40-49	121	1.11 (0.69,1.78)
	60-69	118	1.22 (0.79,1.89)
	70+	87	0.63 (0.35,1.14)
Gender (compared to female)	Male	112	1.31 (0.88,1.94)
Side (compared to left)	Right	313	1.19 (0.89, 1.57)
CEAP (compared to CEAP stage C2-3)	CEAP stage C4-6	62	1.57 (0.91, 2.73)

Gonzalez-Zeh 2008

Gonzalez-Zeh 2008[37] evaluated the baseline patient-related factors influencing reflux one year after foam sclerotherapy.

Multivariable logistic regression analysis (Table 35) was used to assess risk factors for reflux. It showed that for foam sclerotherapy (n=53), no non specialist assessable factors predicted reflux without high levels of uncertainty about the direction of effect.

Table 35: Factors assessed for effects on the odds of reflux at one year

Variable	OR (95% CI)
clinical groups C4-6 (compared to C2-3[a])	0.89(0.39, 2.20)
VCSS[b]	0.97(0.44, 2.15)
Age[b]	0.99(0.91, 1.08)

(a) Unclearly reported
(b) Although not stated, likely that the ORs for reflux for the continuous variables (age, VCSS) are per increment increase in those variables

Thomasset 2010

Thomasset 2010[102] assessed factors associated with complete occlusion of the target vein on duplex analysis at follow-up, and also factors associated with complications. The analysis was poorly reported though it seems univariate analyses for the 8 risk factors were performed. Although this study did not meet the inclusion criterion of having a multivariable analysis, because only one risk factor was significant on univariate testing, a multivariable analysis would have been an unnecessary next step, so this study has been included.

For the outcome of complete occlusion of the target vein, the only risk factor associated was compliance with post-procedure compression hosiery (p<0.05). No effect sizes were presented. This is not a factor that could be ascertained pre-treatment and so has little value in making a pre-treatment prediction about which patients will do well. Patients could be asked before treatment if they'd be compliant with stockings after treatment, but this would be unlikely to produce a valid indication of actual post-operative compliance.

For the outcome of any complication, female gender was associated with a greater risk (p<0.05). No effect size was reported. For each complication considered separately, female gender was associated with skin staining (P<0.05). Again, no effect sizes were given. There were no associations between female gender and any other complications considered singly.

6.2.1.1.4 Predictors of outcome after foam sclerotherapy or stripping (combined analysis)

Islamoglu 2011

Islamoglu 2011[43] assessed the baseline factors affecting 2 separate outcome measures of treatment efficacy, on patients undergoing either stripping or foam sclerotherapy with crossectomy. The time of follow-up was a mean (sd) of 10.2(5.1) months.

The multivariable results for each outcome (Table 36 and Table 37) were all adjusted for treatment type, and so the results for each treatment cannot be presented separately. However because treatment type did not significantly affect outcome, the results can be applied validly to either treatment.

Post-op symptom recurrence at 10 months

Pre-op unilateral symptoms (i.e. only one leg affected), a pre-op CEAP ≥ 3 and family history all increased the odds of symptom recurrence at 10 months after adjustment for treatment type.

Table 36: Factors affecting odds of symptom recurrence (Islamoglu 2011)

Variable	OR (95% CIs)
Unilateral symptoms (versus bilateral)[a]	2.38 (1.68, 3.36)
Pre-op CEAP ≥3 (versus <3)	3.30 (1.90, 5.73)
No family history (versus a family history)	0.36 (0.20, 0.64)

(a) There is poor reporting of results in this paper, with results in the text conflicting with tabular data. The tabular data have been used in this review. Unilateral symptoms affect one leg; bilateral symptoms affect both legs

Post-operative CEAP < 3 at 10 months

Pre-operative unilateral symptoms (i.e. only one leg affected) increased the odds of a post-operative CEAP of <3, but the direction of effect for the other variables had a high level of uncertainty.

Table 37: Factors affecting odds of post-operative CEAP <3 (Islamoglu 2011)

Variable	OR (95% CIs)
Unilateral symptoms (versus bilateral)[b]	2.50 (1.34, 4.66)
Pre-operative CEAP <3 (versus ≥3)	1.445 (0.37, 4.82)
male (versus female)	1.542 (0.20, 3.36)
No previous DVT (versus previous DVT)	2.827 (0.83, 9.62)[a]
Age <60 (versus >60)	1.215 (0.26, 4.01)

(a) This was reported as having a p value of 0.007 in the paper, though this is clearly inconsistent with the 95% CIs.
(b) Unilateral symptoms affect one leg; bilateral symptoms affect both legs

6.2.2 Economic evidence

No cost effectiveness evidence was identified for this question.

6.2.3 Evidence statements

6.2.3.1 Clinical

Surgery

Quality of life

- One study comprising 203 participants found that **recurrent disease** at baseline was associated with **worse** quality of life at 6 months after surgery than no recurrent disease at baseline [LOW QUALITY]
- One study comprising 203 participants found that **CEAP stage C4** at baseline was associated with **worse** quality of life at 6 months after surgery than other CEAP grades at baseline [LOW QUALITY]
- One study comprising 203 participants found that **previous GSV surgery** at baseline was associated with **better** quality of life at 2 years after surgery than no previous GSV surgery at baseline [LOW QUALITY]
- One study comprising 203 participants found that **CEAP stage 5** at baseline was associated with **worse** quality of life at 2 years after surgery than other CEAP grades at baseline [LOW QUALITY]

Reflux recurrence

- One study comprising 1638 participants' legs found that **BMI>29** at baseline was associated with **greater** recurrence of reflux at 6.6 years after surgery than BMI ≤29 at baseline [MODERATE QUALITY]
- One study comprising 1638 participants' legs found that **prior parity** at baseline was associated with **greater** recurrence of reflux at 6.6 years after surgery than no prior parity at baseline [MODERATE QUALITY]

Endovenous Laser Ablation

Reflux

- One study comprising 45 participants found that **CEAP stage C4-6** at baseline was associated with **more** reflux at 1 year after laser ablation than CEAP Stage C2-3 at baseline, but there was considerable uncertainty about the direction of this effect [LOW QUALITY]
- One study comprising 45 participants found that a higher **VCSS score** at baseline was associated with **less** reflux at 1 year after laser ablation, but there was considerable uncertainty about the direction of this effect [LOW QUALITY]
- One study comprising 45 participants found that **age** at baseline **did not predict** reflux at 1 year after laser ablation [LOW QUALITY]

DVT

- One study comprising 210 participants' legs found that DVT at 2-4 days after laser ablation was not associated with any non-specialist assessable factor [VERY LOW QUALITY].

Recanalisation

- One study comprising 210 participants' legs found that recanalisation 2-11 months after laser ablation was not associated with any non-specialist assessable factor [VERY LOW QUALITY].

Foam sclerotherapy

Reflux

- One study comprising 53 participants found that **CEAP stage C4-6** at baseline was associated with **less** reflux at 1 year after foam sclerotherapy than CEAP stage C2-3, but there was considerable uncertainty about the direction of this effect [LOW QUALITY].
- One study comprising 53 participants found that the **VCSS score** at baseline did not predict reflux at 1 year after foam sclerotherapy [LOW QUALITY].
- One study comprising 53 participants found that **age** at baseline did not predict reflux at 1 year after foam sclerotherapy [LOW QUALITY].

Reflux recurrence

- One study comprising 807 participants' veins found that **age <40** at baseline was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than age 50-59 at baseline [MODERATE QUALITY].
- One study comprising 807 participants' veins found that **age 40-49** at baseline was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than age 50-59 at baseline, but there was considerable uncertainty about the direction of this effect [MODERATE QUALITY].
- One study comprising 807 participants' veins found that **age 60-69** at baseline was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than age 50-59 at baseline, but there was considerable uncertainty about the direction of this effect [MODERATE QUALITY].
- One study comprising 807 participants' veins found that **age 70+** at baseline was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than age 50-59 at baseline, but there was considerable uncertainty about the direction of this effect [MODERATE QUALITY].
- One study comprising 807 participants' veins found that being **male** was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than being female, but there was considerable uncertainty about the direction of this effect [MODERATE QUALITY].
- One study comprising 807 participants' veins found that being **right leg-affected** at baseline was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than being left leg-affected at baseline, but there was considerable uncertainty about the direction of this effect [MODERATE QUALITY]).
- One study comprising 807 participants' veins found that being **CEAP stage C4-6** at baseline was associated with a **greater** likelihood of reflux recurrence at a particular point in time after foam sclerotherapy than being CEAP stage C2-3 at baseline, but there was considerable uncertainty about the direction of this effect [MODERATE QUALITY].

Any complications

- One study comprising 116 participants' veins found that **being female** was associated with a **greater** likelihood of any complications after foam sclerotherapy than being male [VERY LOW QUALITY].

Skin staining

- One study comprising 116 participants' veins found that **being female** was associated with a **greater l**ikelihood of skin staining after foam sclerotherapy than being male [VERY LOW QUALITY].

Analysis common to stripping surgery and foam sclerotherapy with crossectomy (adjusted for treatment effect)

Symptom recurrence

- One study comprising 372 participants found that symptoms affecting only one leg at baseline were associated with greater symptom recurrence at 10.2 months than symptoms affecting both legs at baseline [VERY LOW QUALITY].
- One study comprising 372 participants found that symptoms on one leg at baseline were associated with greater symptom recurrence at 10.2 months compared to symptoms on both legs at baseline [VERY LOW QUALITY].
- One study comprising 372 participants found that pre-op CEAP ≥3 at baseline was associated with greater symptom recurrence at 10.2 months than pre-op CEAP <3 at baseline [VERY LOW QUALITY].
- One study comprising 372 participants found that having no family history of venous disease at baseline was associated with lower symptom recurrence at 10.2 months than having a family history of venous disease at baseline [VERY LOW QUALITY].

Post op CEAP <3

- One study comprising 372 participants found that symptoms affecting one leg at baseline was associated with greater odds of post op CEAP <3 at 10.2 months than symptoms affecting both legs at baseline [VERY LOW QUALITY].
- One study comprising 372 participants found that pre-op CEAP <3 at baseline was associated with greater odds of post op CEAP <3 at 10.2 months than pre-op CEAP ≥3 at baseline, but there was considerable uncertainty about the direction of this effect [VERY LOW QUALITY].
- One study comprising 372 participants found that being male was associated with greater odds of post op CEAP <3 at 10.2 months than being female, but there was considerable uncertainty about the direction of this effect [VERY LOW QUALITY].
- One study comprising 372 participants found that no previous DVT at baseline was associated with greater odds of post op CEAP <3 at 10.2 months than a previous history of DVT at baseline, but there was considerable uncertainty about the direction of this effect [VERY LOW QUALITY].
- One study comprising 372 participants found that age <60 at baseline was associated with greater odds of post op CEAP <3 at 10.2 months than age >60 at baseline, but there was considerable uncertainty about the direction of this effect [VERY LOW QUALITY].

6.2.3.2 Economic

- No cost effectiveness evidence was identified for this question.

Recommendation	**3. Refer people with bleeding varicose veins to be seen by a vascular service immediately or within 24 hours.** **4. Refer people with a recent history of minor bleeding from varicose veins to be seen by a vascular service within 2 weeks.** **5. Refer people to a vascular service if they have:** • **symptomatic primary or recurrent varicose veins or** • **lower-limb skin changes (such as pigmentation or eczema) thought to be caused by chronic venous insufficiency.** **6. Refer people with superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected superficial venous incompetence to a vascular service.** **7. Refer people to a vascular service if they have:** • **a venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks) or** • **a healed venous leg ulcer.**

6.3 Recommendations and link to evidence

Research recommendation	**1. In people with varicose veins at CEAP (Clinical, etiological, anatomical and pathophysiological) stage C2 or C3, what are the factors that influence progression of the disease to CEAP stages C5 or C6?** **2. Is pelvic venous incompetence related to recurrence and symptoms of varicose veins?**
Relative values of different outcomes	Progression through the CEAP stages, health related quality of life and patient-assessed symptoms (including pain, discomfort, body image concerns, swelling, aching, and heaviness) were considered by the GDG to be the most important outcomes to identify which people would benefit from a referral to a vascular service. Other important outcomes were physician reported severity or disability score, need for further treatment, presence of reflux, complications from varicose veins and adverse events from interventions.
Trade-off between clinical benefits and harms	The evidence for these recommendations comes from two prognostic reviews: • What factors predict progression of varicose veins? (section 6.1) This was to enable the GDG to identify evidence that indicated which people are at risk of progression at any stage of disease to more severe disease and to prioritise these people for referral. • What factors predict increased benefits or harms from varicose veins interventional treatment? (section 6.2). This was to enable the GDG to identify any prognostic factors that are associated with better or worse outcomes after

interventional treatments, which may affect the referral decision.

Any factors identified that increase the risk of disease progression and/or indicate treatment is likely to be of benefit would be good markers for referral. Timely appropriate referral and intervention prevent disease progression, alleviate symptoms and disability.

The evidence reviewed for the progression of varicose veins through the CEAP stages, identified the following factors as significant risk factors:

Progression through the CEAP stages: greater age, body mass index (BMI) greater than 25, and a patient-reported sense of swelling in the lower leg.

Progression to ulceration (CEAP stage C6): male gender, and a past history of leg injury (defined as a serious leg injury such as a broken leg, burn, stab or gunshot wound or a crush injury)

The evidence reviewed for the predicting benefits or harms from varicose veins interventional treatment, identified the following factors as significant risk factors:

Stripping surgery

In the shorter term (6 months), **recurrent disease at baseline** was associated with a poorer quality of life after surgery compared to non-recurrent varicose veins after adjusting for baseline quality of life. However, in the longer term (2 years**) previous GSV surgery** was associated with a better baseline-adjusted quality of life.

CEAP stage C4-5 at baseline was associated with a poorer baseline-adjusted quality of life after surgery compared to other CEAP stages at baseline.

A **BMI greater than 29** was associated with greater recurrence of reflux after surgery compared with a BMI of less than 29.

Endothermal ablation

There was only evidence identified for the presence of reflux and no factors were found which predicted greater reflux after endothermal ablation.

Foam sclerotherapy

No factors were found which predicted greater reflux after foam sclerotherapy.

Being **female** was associated with an increased risk of complications after foam sclerotherapy compared with being male.

Stripping surgery or foam sclerotherapy with crossectomy

Having **varicose veins in one leg** was associated with greater symptom recurrence than having varicose veins in both legs after treatment, in a combined analysis of surgery and foam sclerotherapy. However it was also found that having **varicose veins in one leg** was associated with greater odds of a CEAP stage of less than 3 after treatment. These findings are clearly contradictory and prohibit any recommendation based on presence of varicose veins in only one leg.

Having **CEAP stage 3 or over**, was associated with greater symptom recurrence than having a CEAP stage of less than 3 after treatment, in a combined analysis of surgery and foam sclerotherapy.

Having a **family history** of venous disease was associated with a greater symptom recurrence than no family history of venous disease after treatment, in a combined analysis of surgery and foam sclerotherapy.

The evidence was very limited in identifying factors that can be assessed by a non-specialist prior to referral to a vascular service. Important factors that would help assessment for referral were not measured in the studies (such as pain). The factors identified were unhelpful as markers on their own in identifying who would benefit or not benefit from treatment (such as gender, age, family history).

The only identified modifiable risk factor which was associated both with a higher

	risk progression of varicose veins and a predicted a worse outcome after treatment was BMI >29. This has been discussed in the recommendation about providing patient information (section 5.5)
Economic considerations	The GDG discussed the economic implications associated with referral at different stages of varicose veins. It was expected that referral would be cost-effective for the individuals described in this recommendation as they would benefit most from an early intervention. Treatment is likely to reduce the likelihood of disease progression and improve quality of life by reducing symptoms.
Quality of evidence	Four studies were identified that provided evidence for the prognostic review identifying risk factors for the progression through the CEAP stages. These studies ranged in quality from low to very low quality. Main limitations of the progression data were that most were from case-control studies, which rely on participant recall for risk factor status. Seven studies were identified that provided evidence for the prognostic review identifying factors that predicted increased benefits or harms from interventional treatment. These studies ranged in quality from moderate to very low quality. The main limitations of these data were poor reporting of multivariate methods and unclear levels of attrition bias. The GDG noted that there were many problems with the evidence including: - many of the potential risk factors which could aid a GP have not been measured in studies - the body of evidence was poor quality, patchy and contradictory - the evidence was not based on rigorous multivariate analysis which considered all potential confounders was excluded thereby reducing the evidence base
Other considerations	In the absence of any clear markers of disease progression and likely treatment benefit, and thus indicators of referral, the GDG based the recommendation on the limited evidence and consensus. **Vascular service** The GDG discussed where people should be referred to. They agreed that referral should be to a vascular service, defined as: *'a team of healthcare professionals who have the skills to undertake a full clinical and duplex Doppler ultrasound assessment and provide a full range of treatment.'* They wanted to highlight that the location of this service can be decided locally with some of the service being delivered in primary care where skills and equipment are available. The GDG agreed that the clinical benefits of referring people to a vascular service were considered to be: • Availability of a differential diagnosis • The cost-effectiveness of conservative treatments normally given before referral are questionable • Access to cost-effective treatments • Access to specialist information and advice The GDG wanted to highlight that these recommendations are about referral and not everyone referred would receive interventional treatment. The GDG agreed that people who weren't treated would still gain benefit from the vascular specialist in terms of obtaining specialist assessment and the provision of expert advice and reassurance. **NICE 2001 referral guidelines** NICE produced referral guidance for varicose veins in 2001[64]. Whilst this guideline is intended to replace them, the lack of clear evidence for referral led the GDG to

review the 2001 guidance and use them to help direct their discussions.

As detailed in section 1.1, the GDG have not used the CEAP classification to identify who should be referred. They noted that the classification was not designed as a measure of clinical change, or to provide referral criteria and that there is still uncertainty about how the stages interact with each other The GDG agreed that it was more important for those referring to a vascular service to use clear, key clinical indicators and listen to the person presenting rather than trying to categorise people using CEAP..

As detailed in section 1.1, the GDG have not used the CEAP classification to identify who should be referred but used key clinical indicators. They noted that the classification was not designed as a measure of clinical change, or to provide referral criteria and that there is still uncertainty about how the stages interact with each other.

Symptomatic varicose veins

The GDG agreed that all patients with symptomatic varicose veins should be referred to a vascular service. Symptomatic varicose veins were defined as: '*those found in association with troublesome lower limb symptoms (typically pain, aching, discomfort, swelling, heaviness and/or and itching) that are thought to be due to the effects of superficial venous reflux and for which no other more likely cause is apparent.'*

The decision to refer patients with symptomatic varicose veins was based partially on the evidence from the review of interventional treatments (Chapter 9). The results of this review and subsequent cost effectiveness analysis showed that interventional treatment is cost effective for the patients included within the clinical trials reviewed. Sixteen (16) studies of interventional treatment provided details of CEAP stages of patients included in the study. The percentage of patients with CEAP stage C2-C3 disease ranged from 47-98%. Thirteen of these studies (81%) had over 70% of patients with CEAP stage C2-C3 disease and six studies (38%) included more than 90% of patients with CEAP stage C2-C3 disease. Where there are data for C2 disease alone, these patients comprised 69% (1458/2112) of all study participants. However, none of the studies provided sub-group analyses of treatment effect by baseline CEAP stage or any other baseline characteristic (e.g. pain score, symptoms, which truncal branches were treated etc.) There was, therefore, no way of determining who would benefit 'most' from interventional treatment. All the GDG could say was that, as the majority of patients in the clinical trials used in the economic analysis were CEAP stage C2 and C3 disease, the results have to be assumed to be applicable to patients with this stage of disease.

Whilst the GDG were keen to not be seen to make a recommendation about cosmetic surgery on the NHS, they were apprehensive about making a judgement on the impact of cosmetic concerns on the individual. They felt that the impact that varicose veins has on the quality of a patient's life should be explored individually when deciding the best course of action.

Lower limb skin changes (such as pigmentation or eczema) thought to be due to chronic venous insufficiency

Patients with skin changes in legs affected by venous hypertension are at greater risk of developing venous leg ulceration and should be referred to a vascular service. The GDG felt this patient group were often under referred and that patients with lower limb skin changes should be referred so that prophylactic treatment can be planned if appropriate.

The recommendation referring patients with symptomatic varicose veins and lower limb skin changes thought to be due to chronic venous insufficiency to the vascular service was identified by the GDG as a key priority for implementation. They felt that this recommendation would have a high impact on outcomes important for patients. It was hoped that this would reduce the number of more severe venous

leg problems such as leg ulcer, and would improve the quality of life for patients. They anticipate it will have a high impact on reducing variation in care.

Bleeding varicose veins or a recent history of bleeding varicose veins

Bleeding from varicose veins may be life threatening and warrants immediate first aid and treatment within 24 hours. Depending on the severity, people with bleeding varicose veins should be seen by a vascular service immediately or within 24 hours.

Where a person has a recent history of minor bleeding from their varicose veins, the GDG were concerned about the risk of future more serious bleeding and agreed that they should be seen by a vascular service within 2 weeks.

Superficial vein thrombosis

The GDG were aware of evidence which indicated that DVT was present in approximately 20% of legs with superficial vein thrombosis, which needed evaluation and may need appropriate treatment. Some members of the GDG highlighted the problems with identifying superficial vein thrombosis and so a definition was included.

Active and healed venous leg ulcers

A break in the skin below the knee failing to heal within 2 weeks suggests underlying arterial or venous disease is probable and requires expert help. As ulcers of longer duration are more difficult to heal the GDG recommended referral and referral within 2 week if the leg ulcer is active. This recommendation is consistent with the recommendation in the NICE 2001 referral guidelines.

The GDG identified the recommendation for referring people with active or healed venous leg ulcers as a key priority for implementation. The GDG felt that there was a lack of awareness that the risk of leg ulcer recurrence could be reduced by interventional treatment and that implementing this recommendation would have a high impact on outcomes important to patients, would reduce variation in care and set challenging but achievable expectations of the health service.

Research recommendations

The GDG were concerned that there was still much about the natural progression of varicose veins which was unknown. Therefore they felt that that the following research recommendation in this area was a high priority in order to further understanding. Further details can be found in appendix N.

What is the natural progression of varicose veins through to CEAP stage 6 and what factors influence it?

In addition, a further research recommendation about the relationship between pelvic venous incompetency and varicose veins was felt to be important to further understanding of the natural history of varicose veins.

1

7 Assessment prior to treatment

Historically, veins have been investigated using venography, which is a test using X-ray, needles and contrast agents. Over the last 20-30 years, non-invasive techniques have been developed which have distinct advantages over such invasive techniques.

Duplex ultrasonography (also known as duplex ultrasound or duplex imaging) is a form of medical ultrasonography which uses the two components of grayscale ultrasound and Doppler ultrasound to image the blood vessels of the body. Information on both structure and flow of blood in both arteries and veins is provided in a painless non-invasive manner. Venous duplex ultrasonography may be performed in a vascular laboratory, X-ray department or an outpatient clinic setting with a vascular scientist, radiologist or vascular surgeon performing the procedure. The investigation may take 15-30 minutes or longer depending on the detail of the assessment and who performs the procedure.

When used to assess the veins in the lower limb, duplex ultrasonography is able to assess both the deep, superficial and perforating veins to give important information on anatomical patterns of veins, vein patency, vein diameters and valve function. Such highly detailed information may help decide the type of treatment considered most appropriate, especially when considering minimally invasive endovenous procedures. The source of filling of all superficial veins is also vital information provided by duplex ultrasound, as failure to identify and treat all sources of venous filling is likely to result in recurrence of varicosities. Duplex ultrasound may therefore help in the pre-operative phase by mapping all varicose veins, tributaries and incompetent perforating veins.

On a clinical basis, duplex ultrasound scanning is firmly established as the gold standard measure for assessing venous disease in the lower limb. Despite this, hand held Doppler ultrasound is still used for this purpose in some clinics. This is on the basis that some clinicians believe it to be an adequate substitute for the more expensive and time-consuming duplex ultrasound, although hand held Doppler does not have the advantages of the grayscale ultrasound, which facilitates assessment of both the superficial and deep veins. This variation in practice necessitates a diagnostic review.

As duplex ultrasound has been chosen as the gold standard in this review, the assumption is that it is the superior measure. Hence showing that hand held Doppler has *greater* diagnostic accuracy than duplex ultrasound is not possible because any discrepancies between the two techniques will automatically be attributed to the superiority of the gold standard. It is only be possible to show whether hand held Doppler is an acceptable proxy for duplex ultrasound or not. In other words, is the margin of diagnostic error inherent with hand held Doppler at an acceptable level, such that hand held Doppler could be used in certain circumstances where it is not possible to use duplex ultrasound? The aim of the first part of this section (7.1) is to review the literature assessing the diagnostic accuracy of hand held Doppler relative to duplex ultrasound.

Furthermore, as the most clinically relevant indication of duplex ultrasound is its effect on clinical outcomes following treatment, the second aim of this section (7.2) is to review the literature assessing the effect on outcomes of duplex assessment prior to interventional treatment compared to interventional treatment alone.

7.1 Review question: What is the diagnostic accuracy of hand held Doppler compared to duplex scanning in patients with varicose veins?

For full details see review protocol in appendix C.

Table 38: PICO characteristics of review question

Population	Adults with leg varicose veins.
Index tests	Hand held Doppler ultrasound testing for venous reflux
Reference standard	Duplex ultrasound scanning for venous reflux
Outcomes	• Sensitivity (%) and specificity (%), for particular threshold(s) • Positive/negative predictive value • Positive/negative predictive value • Positive/ negative diagnostic likelihood ratios • Post-test probability (at a set pre-test probability)
Study design	Diagnostic studies

7.1.1 Methodology – diagnostic data analysis

Data and outcomes

The following outcomes were reported whenever they were provided in a study or it was possible to derive them from the study data: sensitivity, specificity, and positive or negative predictive values. In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data to allow calculation of these accuracy measures.

Several different veins were evaluated by different studies. As the diagnostic accuracy of hand held Doppler in relation to duplex may depend on the location and dimensions of the vein, each vein was evaluated and reported separately.

A variety of diagnostic thresholds were used by studies. For both duplex and hand held Doppler, two different reflux thresholds of >0.5 and >1 second were reported in different studies, and sometimes different thresholds were used for duplex and hand held Doppler within the same study. These thresholds represent the minimum duration of any reflux, and will influence the sensitivity and specificity of the measures. A longer threshold (i.e. >1 second) will be less sensitive than a shorter one as it won't pick up any true reflux lasting <1 second, but it will also pick up less false positives as noise is less likely to last > 1 second. In contrast, a shorter threshold (i.e. >0.5 seconds) will be more sensitive as it will pick up more true positives, but may also pick up more noise and so more false positives. Hence if a study uses a threshold of 0.5 seconds for duplex ultrasound and a threshold of 1 second for hand held Doppler, hand held Doppler may be measured as more specific and less sensitive than it might if duplex ultrasound had a threshold of 1 second and hand held Doppler had a threshold of 0.5 seconds. In view of these important effects on interpretation, results have been categorised by the thresholds used in the studies.

Appraising the quality of evidence for diagnostic studies

Evidence for diagnostic data was evaluated by study, using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists, as described in Chapter 3. Quality rating started at HIGH, and each major limitation (Table 5) brought the rating down by one level to a minimum grade of LOW, as explained for interventional studies.

Meta-analysis of data

A diagnostic meta-analysis was not carried out for any outcome, as this requires a minimum of 5 studies per outcome.

7.1.2 Clinical evidence

Summary of included studies

12 diagnostic studies[16,21,24,47,48,57,88,89,91,92,103,105] were found that made the above comparison. Table 39 summarises the characteristics of these studies, and Table 40 contains the overall results in GRADE format. See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 39: Summary of diagnostic studies included in the review

STUDY	Patients (legs)	Population	Reflux locations studied	Reflux threshold hand held Doppler (seconds)	Reflux threshold duplex (seconds)	Methodological quality (comments in brackets indicate where QUADAS2 criteria were NOT met)
Campbell 1997[16]	85(122)	No previous treatments; CEAP status unclear	GSV, popliteal fossa	1	1	Very serious limitations (not stated that reference test was not interpreted with prior knowledge of index test; conduct of index test could have introduced bias – expertise of assessors not clear; test interval unclear)
Darke 1997[21]	73(100)	Treatment history and stage of disease unclear	GSV, SSV	Not stated	0.5	Very serious limitations (conduct of index test could have introduced bias – expertise of assessors not clear; test interval unclear)
De Palma 1993[24]	40(80)	28% with previous stripping; CEAP status unclear	SFJ, SFJ in sub-group with previous stripping	Not stated	Not stated	Very serious limitations (conduct of index test could have introduced bias – expertise of assessors not clear; test interval unclear)
Kent 1998[47]	72(108)	No previous treatment; mostly C2	SFJ, GSV, perforators, SPJ, popliteal veins	0.5	1	No serious limitations
Kim 2000[48]	44(70)	No previous treatment; mostly C2	SFJ, GSV, SPJ	0.5	1	Serious limitations (conduct of index test could have introduced bias - carried out by house officer)
Mercer 1998[57]	61(81)	Treatment history and stage of disease unclear	SFJ, SPJ, Thigh perforators	0.5	0.5	Very serious limitations (reference test interpreted with prior knowledge of index test; test interval unclear)
Rautio 2002B[89]	49(62)	No previous treatment; VDS 0-1	SFJ, GSV at mid-thigh, popliteal	1	1	No serious limitations

STUDY	Patients (legs)	Population	Reflux locations studied	Reflux threshold hand held Doppler (seconds)	Reflux threshold duplex (seconds)	Methodological quality (comments in brackets indicate where QUADAS2 criteria were NOT met)
			fossa and calf			
Rautio 2002A[88]	111(142)	No previous treatments; mostly C2-3	SFJ, SPJ, GSV at upper thigh, lower thigh and calf	1	1	No serious limitations
Salaman 1995[91]	42(72)	Treatment history and stage of disease unclear	SFJ, SPJ, Thigh perforator, calf/ankle perforator, common femoral, popliteal	Not stated	0.5	Very serious limitations (not stated that reference test was not interpreted with prior knowledge of index test; test interval unclear)
Schultheiss 1997[92]	19(19)	No information given on previous treatment; mostly C4	Perforating veins	Not stated	0.5	Very serious limitations (conduct of index test could have introduced bias – expertise of assessors not clear; test interval unclear)
Van der Heiden 1993[103]	48(68)	21% with previous stripping; CEAP status unclear	SFJ, GSV, SSV, Perforating veins, SPJ	Not stated	0.5	Very serious limitations (conduct of index test could have introduced bias – expertise of assessors not clear [surgical residents]; test interval unclear)
Wills 1998[105]	188(315)	39% had received previous treatment; 31% C4 and above	SFJ, SPJ, Perforating veins, Deep veins, SFJ in subset with no skin changes and not recurrent	Not stated	1	Very serious limitations (not stated that reference test was not interpreted with prior knowledge of index test; test interval unclear)

Abbreviations: SFJ=sapheno-femoral junction; SPJ=sapheno-popliteal junction; SSV=short saphenous vein; GSV= great saphenous vein

Table 40: Clinical Evidence Profile (GRADE table): diagnostic accuracy of the hand held Doppler device in relation to the gold standard of duplex in the detection of reflux in different leg veins.

Study characteristics			Quality Assessment				Summary of findings				
No. of studies	Design	No. of patients (legs)	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Quality
SFJ; threshold of 0.5 second hand held Doppler and 1 second duplex											
2 Kent1998[47] Kim 2000[48]	CS	116 (178)	S[a]	N	N	S[b]	 0.93(0.85-0.98) 0.97(0.86-1.00)	 0.91(0.76-0.98) 0.73(0.54-0.87)	 0.96(0.89-0.99) 0.80(0.66-0.89)	 0.85(0.71-0.94) 0.96(0.81-0.99)	LOW
SFJ; threshold of 1 sec hand held Doppler and 1 sec duplex											
2 Rautio 2002B[89] Rautio2002A[88]	CS	160 (204)	N	N	N	S[b]	 0.65(0.49-0.78) 0.56(0.46-0.66)	 0.93(0.66-1.00) 0.97(0.86-1.00)	 0.97(0.84-0.99) 0.98(0.91-1.00)	 0.45(0.29-0.62) 0.44(0.34-0.55)	MODERATE
SFJ; threshold of 0.5 sec hand held Doppler and 0.5 seconds duplex											
1 Mercer 1998[57]	CS	61 (81)	VS[a]	N	N	S[b]	 0.73(0.60-0.84)	 0.93(0.78-0.99)	 0.96 (0.85-0.99)	 0.64 (0.50-0.76)	VERY LOW
SFJ; incomplete threshold information											
4 DePalma 1993[24] van der Heijden 1993[103] Salaman 1995[91]	CS	318 (535)	VS[a]	S[c]	N	S[b]	 0.48(0.34-0.63) 0.96(0.85-0.99) 0.92(0.82-0.98)	 0.83(0.65-0.94) 0.95(0.76-1.00) 0.95(0.74-1.00)	 0.83(0.66-0.92) 0.98(0.89-0.99) 0.98(0.90-0.99)	 0.49(0.36-0.62) 0.91(0.72-0.98) 0.82(0.62-0.93)	VERY LOW

Study characteristics			Quality Assessment				Summary of findings				
No. of studies	**Design**	**No. of patients (legs)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive predictive value (95% CI)**	**Negative predictive value (95% CI)**	**Quality**
Wills 1998[105]							0.71*	0.71*			
SPJ; threshold of 0.5 sec hand held Doppler and 1 sec duplex											
2 Kent1998[47] Kim 2000[48]	CS	116 (178)	S[a]	N	N	S[b]	 0.82(0.57-0.96) 0.80*	 0.80(0.71-0.88) 0.90*	 0.43(0.28-0.61) 0.57*	 0.96(0.89-0.99) 0.97*	LOW
SPJ; threshold of 1 sec hand held Doppler and 1 sec duplex											
1 Rautio2002A[88]	CS	111 (142)	N	N	N	S[b]	 0.23(0.05-0.54)	 0.96(0.90-0.99)	 0.43(0.16-0.75)	 0.91(0.83-0.95)	MODERATE
SPJ; threshold of 0.5 sec hand held Doppler and 0.5 seconds duplex											
1 Mercer 1998[57]	CS	61 (81)	VS[a]	N	N	S[b]	 0.77(0.56-0.91)	 0.94(0.85-0.98)	 0.83 (0.64-0.93)	 0.91 (0.81-0.96)	VERY LOW
SPJ; incomplete threshold information											
3 van der Heijden 1993[103] Salaman 1995[91] Wills 1998[105]	CS	278 (455)	VS[a]	S[c]	N	S[b]	 1.00(0.8-1.00) 0.56(0.31-0.78) 0.36*	 1.00(0.93-1.00) 0.89(0.78-0.96) 0.92*	 1.00(0.78-1)1.00 0.63(0.39-0.82)	 1.00(0.91-1.00) 0.86(0.75-0.93)	VERY LOW

Study characteristics			Quality Assessment				Summary of findings				
No. of studies	**Design**	**No. of patients (legs)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive predictive value (95% CI)**	**Negative predictive value (95% CI)**	**Quality**
GSV; threshold of 0.5 sec hand held Doppler and 1 sec duplex											
2 Kent1998[47] Kim 2000[48]	CS	116 (178)	S[a]	N	N	S[b]	 0.95(0.88-0.99) 0.82*	 0.68(0.46-0.85) 0.92*	 0.91(0.83-0.95) 0.84*	 0.81(0.60-0.92) 0.74*	LOW
GSV; threshold of 1 sec hand held Doppler and 1 sec duplex											
3 Rautio 2002B[89] Rautio2002A[88] Campbell1997[16]	CS	245 (326)	N	S[c]	N	S[b]	 0.49(0.34-0.64) 0.58(0.47-0.68) 0.86*	 0.92(0.64-1) 0.84(0.70-0.93) 0.82*	 0.96 (81-99) 0.87(0.77-0.93)	 0.32 (0.20-0.49) 0.51(0.41-0.62)	LOW
GSV; incomplete threshold information											
2 van der Heijden 1993[103] Darke 1997[21]	CS	121 (168)	VS[a]	N	N	S[b]	 0.91(0.79-0.98) 0.95(0.89-0.99)	 0.96(0.78-1) 1.00(0.75-1.00)	 0.98(0.88-0.99) 1.00(0.95-1.00)	 0.84(0.67-0.94) 0.75(0.52-0.89)	VERY LOW
SSV; incomplete threshold information											
2 van der Heijden 1993[103] Darke 1997[21]	CS	121 (168)	VS[a]	N	N	S[b]	 0.89(0.65-0.99) 0.90(0.70-0.99)	 1.00(0.93-1.00) 0.94(0.86-0.98)	 1.00(0.77-1.00) 0.79(0.59-0.91)	 0.95(0.86-0.99) 0.97(0.91-0.99)	VERY LOW

Study characteristics			Quality Assessment				Summary of findings				
No. of studies	**Design**	**No. of patients (legs)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive predictive value (95% CI)**	**Negative predictive value (95% CI)**	**Quality**
Perforators; threshold of 0.5 sec hand held Doppler and 1 sec duplex											
1 Kent1998[47]	CS	72 (108)	N	N	N	S[b]	0.87(0.6-0.98)	0.26(0.17-0.36)	0.16(0.10-0.25)	0.92(0.76-0.98)	MODERATE
Perforators; threshold of 0.5 sec hand held Doppler and 0.5 seconds duplex											
1 Mercer 1998[57]	CS	61 (81)	VS[a]	N	N	S[b]	0.51(0.34-0.69)	0.85(0.73-0.93)	0.69 (0.5-0.84)	0.73 (0.61-0.82)	VERY LOW
Perforators; incomplete threshold information											
4 van der Heijden 1993[103] Salaman 1995[91] Wills 1998[105] Schultheiss 1997[92]	CS	297 (474)	VS[a]	N	N	S[b]	0.53(0.29-0.76) 0.29(0.04-0.71) 0.44* 0.29*	0.94(0.73-1.00) 0.81(0.69-0.89) 0.79* 0.15*	0.91(0.62-0.98) 0.13(0.04-0.38)	0.65(0.46-0.81) 0.92(0.82-0.96)	VERY LOW
Popliteal veins; threshold of 0.5 sec hand held Doppler and 1 sec duplex											
1 Kent1998[47]	CS	72 (108)	N	N	N	S[b]	0.50(0.23-0.77)	0.90(0.82-0.95)	0.44(0.23-0.67)	0.92(0.85-0.96)	MODERATE
Popliteal veins; incomplete threshold information											
1 Salaman 1995[91]	CS	42 (72)	VS[a]	N	N	S[b]	0.40(0.05-0.85)	0.99(0.92-1.00)	0.67(0.21-0.94)	0.96(0.88-0.99)	VERY LOW
Popliteal fossa (veins not specified); threshold of 1 sec hand held Doppler and 1 sec duplex											

Study characteristics			Quality Assessment				Summary of findings				
No. of studies	**Design**	**No. of patients (legs)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive predictive value (95% CI)**	**Negative predictive value (95% CI)**	**Quality**
1 Campbell 1997[16]	CS	85 (122)	VS[a]	N	N	S[b]	0.72(0.55-0.85)	0.90(0.82-0.96)	0.78(0.62-0.88)	0.87(0.78-0.93)	VERY LOW

Abbreviations: CS= Cross-sectional; N= No serious limitations/inconsistency/imprecision; S= serious limitations/inconsistency/imprecision; VS= Very serious limitations; SFJ=sapheno-femoral junction; SPJ=sapheno-popliteal junction; SSV=short saphenous vein; GSV= great saphenous vein

(a) if there was one methodological limitation in the majority of studies (according to the QUADAS criteria), serious limitations were given. If there were two or more limitations in the majority of studies (according to the QUADAS criteria), very serious limitations were given. For details of the actual limitations observed, see evidence tables in appendix G.

(b) If the 95% CIs spread by >+0.1 in the majority of studies in an outcome then a rating of serious imprecision was given

(c) If there was no or minimal overlap between 95% CIs across studies in an outcome then a rating of serious inconsistency was given

**95% CIs and/or +ve and –ve predictive values were not calculable due to insufficient raw data presented in the paper. For Kim 2000, the sample size and point estimates for sensitivity, specificity, and +ve and –ve predictive values were presented, which should have allowed calculation of raw values, and subsequent derivation of 95% CIs. However, it was not possible to calculate the raw values from the data for 2 of the 3 outcomes in that study, as the raw values yielded were not coherent with the original data. This suggests errors in the data presented by Kim 2000.*

7.1.3 Economic evidence

Published literature

No cost effectiveness evidence was identified for this question.

7.1.4 Evidence Statements

7.1.4.1 Clinical

Diagnostic accuracy of hand held Doppler in the detection of leg venous reflux with reference to duplex

Sapheno-femoral junction (SFJ)

Threshold of 0.5 seconds hand held Doppler and 1 second duplex

- Two studies comprising 178 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.93 to 0.97 and a specificity ranging from 0.73 to 0.91 [LOW QUALITY].

Threshold of 1 second hand held Doppler and 1 second duplex

- Two studies comprising 204 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.56 to 0.65 and a specificity ranging from 0.93 to 0.97 [MODERATE QUALITY].

Threshold of 0.5 seconds hand held Doppler and 0.5 second duplex

- One study comprising 81 patients' legs suggested that hand held Doppler had a sensitivity of 0.73 and a specificity of 0.93 [VERY LOW QUALITY].

Incomplete threshold information

- Four studies comprising 535 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.48 to 0.96 and a specificity ranging from 0.71 to 0.95 [VERY LOW QUALITY].

Sapheno-popliteal junction (SPJ)

Threshold of 0.5 seconds hand held Doppler and 1 second duplex

- Two studies comprising 178 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.80 to 0.82 and a specificity ranging from 0.80 to 0.90 [LOW QUALITY].

Threshold of 1 second hand held Doppler and 1 second duplex

- One study comprising 142 patients' legs suggested that hand held Doppler had a sensitivity of 0.23 and a specificity of 0.96 [MODERATE QUALITY].

Threshold of 0.5 seconds hand held Doppler and 0.5 second duplex

- One study comprising 81 patients' legs suggested that hand held Doppler had a sensitivity of 0.77 and a specificity of 0.94 [VERY LOW QUALITY].

Incomplete threshold information

- Three studies comprising 455 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.36 to 1 and a specificity ranging from 0.89 to 1 [VERY LOW QUALITY].

Great Saphenous Vein

Threshold of 0.5 seconds hand held Doppler and 1 second duplex

- Two studies comprising 178 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.82 to 0.95 and a specificity ranging from 0.68 to 0.92 [LOW QUALITY].

Threshold of 1 second hand held Doppler and 1 second duplex

- Three studies comprising 326 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.49 to 0.86 and a specificity ranging from 0.82 to 0.92 [LOW QUALITY].

Incomplete threshold information

- Two studies comprising 168 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.91 to 0.95 and a specificity ranging from 0.96 to 1 [VERY LOW QUALITY].

Short Saphenous vein

Incomplete threshold information

- Two studies comprising 168 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.89 to 0.90 and a specificity ranging from 0.94 to 1 [VERY LOW QUALITY].

Perforators

Threshold of 0.5 seconds hand held Doppler and 1 second duplex

- One study comprising 108 patients' legs suggested that hand held Doppler had a sensitivity of 0.87 and a specificity of 0.26 [MODERATE QUALITY].

Threshold of 0.5 seconds hand held Doppler and 0.5 second duplex

- One study comprising 81 patients' legs suggested that hand held Doppler had a sensitivity of 0.51 and a specificity of 0.85 [VERY LOW QUALITY].

Incomplete threshold information

- Four studies comprising 474 patients' legs suggested that hand held Doppler had a sensitivity ranging from 0.29 to 0.53 and a specificity ranging from 0.15 to 0.94 [VERY LOW QUALITY].

Popliteal veins

Threshold of 0.5 seconds hand held Doppler and 1 second duplex

- One study comprising 108 patients' legs suggested that hand held Doppler had a sensitivity of 0.50 and a specificity of 0.90 [MODERATE QUALITY].

Incomplete threshold information

- One study comprising 72 patients' legs suggested that hand held Doppler had a sensitivity of 0.40 and a specificity of 0.99 [VERY LOW QUALITY].

Popliteal fossa (vein not specified)

Threshold of 1 second hand held Doppler and 1 second duplex

- One study comprising 122 patients' legs suggested that hand held Doppler had a sensitivity of 0.72 and a specificity of 0.90 [VERY LOW QUALITY].

7.1.4.2 Economic

No cost effectiveness evidence was found for this question.

7.2 Review question: Does the use of duplex ultrasound during assessment improve outcome after interventional treatment compared to no duplex scanning in people with leg varicose veins?

For full details see review protocol in appendix C.

Table 41: PICO characteristics of review question

Population	Adults with leg varicose veins.
Intervention/s	Duplex ultrasound assessment prior to surgical, foam sclerotherapy or endothermal treatment
Comparison/s	No duplex ultrasound assessment prior to surgical, foam sclerotherapy or endothermal treatment
Outcomes	• Patient-reported outcome:- ○ Health-related quality of life ○ Patient-assessed symptoms. • Physician-reported outcomes. • Presence of reflux • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work/normal activities
Study design	Systematic Reviews, RCTs, cohort studies.

7.2.1 Clinical evidence

Summary of included studies

Four RCTs were identified through the literature search[7-9,96]. All studies used surgery as the treatment after duplex ultrasound/no duplex ultrasound, and none were found using foam sclerotherapy or endothermal ablation. All studies included some participants with bilateral varicose veins (i.e. both legs affected), and although the unit of randomisation was participants, the unit of analysis was legs rather than participants. Three studies reported on the same project, [7-9] each reporting different outcomes or follow-up points on the same set of participants, although the number of legs analysed varied depending on loss to follow-up. No cohort studies were found.

The studies are summarised in Table 42. See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 42: Summary of studies included in the review

Study	number of patients (legs) analysed at longest follow-up point	CEAP grades	Age (duplex/non-duplex)	Treatments given after duplex	Follow-up
Blomgren 2005[7]	219 (256)	Most were C2-C3, but 51/243 legs were >C3	47.9/44.6	Ligation and stripping of the great saphenous vein and/or small saphenous vein and/or phlebectomies	2 years
Blomgren 2006A[8]	250 (number of legs not given in paper)	Not given, but similar to above (difference due to different number of analysed patients)	not given but similar to above	Ligation and stripping of the great saphenous vein and/or small saphenous vein and/or phlebectomies	2 years
Blomgren 2011[9]	175 (198)	Not given, but similar to above (difference due to different number of analysed patients)	not given but similar to above	Ligation and stripping of the great saphenous vein and/or small saphenous vein and/or phlebectomies	7 years
Smith 2002[96]	149 (189)	Not stated	Not given	Ligation and stripping of the great saphenous vein and/or small saphenous vein and/or phlebectomies	1 year

Table 43. Clinical evidence profile (GRADE table): duplex versus no duplex for varicose veins.

Quality assessment							Proportion with event		Effect		Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	duplex	no duplex	Relative (95% CI)	Absolute	
Operated legs unchanged or worse (patient assessed) compared to baseline – 2 years											
1 Blomgren 2006A[8]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	15/130 (11.5%)	19/120 (15.8%)	RR 0.73 (0.39 to 1.37)	43 fewer per 1000 (from 96 fewer to 58 more)	VERY LOW
Operated legs unchanged or worse (patient assessed) compared to baseline – 7 years											
1 Blomgren 2011[9]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	16/123 (13%)	28/108 (25.9%)	RR 0.5 (0.29 to 0.88)	130 fewer per 1000 (from 31 fewer to 184 fewer)	VERY LOW
SFJ reflux – 6–8 weeks											
2 Blomgren 2005[7], Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/252 (4.4%)	38/263 (14.4%) median event rate: 11.7%	RR 0.3 (0.16 to 0.57)	82 fewer per 1000 (from 50 fewer to 98 fewer)	LOW
SFJ reflux – 2 years											
1 Blomgren 2005[7]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/127 (11%)	44/129 (34.1%)	RR 0.32 (0.19 to 0.56)	232 fewer per 1000 (from 150 fewer to 276 fewer)	LOW
SFJ reflux – 7 years											
1 Blomgren 2011[9]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/95 (11.6%)	38/99 (38.4%)	RR 0.3 (0.16 to 0.55)	269 fewer per 1000 (from 173 fewer to 323 fewer)	LOW

Quality assessment							Proportion with event		Effect		Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	duplex	no duplex	Relative (95% CI)	Absolute	
SPJ reflux – 8 weeks											
1 Blomgren 2005[7]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	4/160 (2.5%)	9/166 (5.4%)	RR 0.46 (0.14 to 1.47)	29 fewer per 1000 (from 46 fewer to 25 more)	VERY LOW
SPJ reflux – 2 years											
1 Blomgren 2005[7]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7/127 (5.5%)	13/129 (10.1%)	RR 0.55 (0.23 to 1.33)	45 fewer per 1000 (from 78 fewer to 33 more)	VERY LOW
SPJ reflux – 7 years											
1 Blomgren 2011[9]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	2/95 (2.1%)	9/99 (9.1%)	RR 0.23 (0.05 to 1.04)	70 fewer per 1000 (from 86 fewer to 4 more)	VERY LOW
GSV reflux – 12 months											
1 Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/92 (8.7%)	9/97 (9.3%)	RR 0.94 (0.38 to 2.33)	6 fewer per 1000 (from 58 fewer to 124 more)	VERY LOW
SSV reflux – 6 weeks											
1 Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	4/92 (4.3%)	6/97 (6.2%)	RR 0.70 (0.20 to 2.41)	19 fewer per 1000 (from 50 fewer to 87 more)	VERY LOW
SSV reflux – 12 months											
1 Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	6/92 (6.5%)	8/97 (8.3%)	RR 0.79 (0.29 to 2.19)	17 fewer per 1000 (from 59 fewer to 99 more)	VERY LOW

Quality assessment							Proportion with event		Effect		Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	duplex	no duplex	Relative (95% CI)	Absolute	
Perforators reflux – 6 weeks											
1 Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/92 (1.1%)	5/97 (5.2%)	RR 0.21 (0.03 to 1.77)	41 fewer per 1000 (from 50 fewer to 40 more)	VERY LOW
Perforators reflux – 12 months											
1 Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	4/92 (4.3%)	15/97 (15.5%)	RR 0.28 (0.1 to 0.82)	112 fewer per 1000 (from 28 fewer to 140 fewer)	VERY LOW
Need for/actual reoperation – 2 years											
1 Blomgren 2005[7]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/145 (2.1%)	14/147 (9.5%)	RR 0.22 (0.06 to 0.74)	74 fewer per 1000 (from 25 fewer to 89 fewer)	LOW
Need for/actual reoperation – 7 years											
1 Blomgren 2011[9]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/124 (12.1%)	38/134 (28.4)%	RR 0.43 (0.25 to 0.74)	162 fewer per 1000 (from 74 fewer to 213 fewer)	LOW
Development of new branch varicosities at 12 months											
1 Smith 2002[96]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/92 (8.7%)	9/97 (9.3%)	RR 0.94 (0.38 to 2.33)	6 fewer per 1000 (from 58 fewer to 124 more)	VERY LOW
Adverse events – DVT											
1	randomised	very serious[a]	no serious	no serious	no serious	none	0/145	0/147 (0%)	not pooled	not pooled	

Quality assessment							Proportion with event		Effect		Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	duplex	no duplex	Relative (95% CI)	Absolute	
Blomgren 2005[7]	trials		inconsistency	indirectness	imprecision		(0%)				LOW
Complications of varicose veins at 7 years – venous ulcer											
1 Blomgren 2011[9]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/70 (0%)	0/88 (0%)	not pooled	not pooled	LOW
Complications of varicose veins at 7 years – pigmentation/eczema											
1 Blomgren 2011[9]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/70 (4.3%)	9/88 (10.2%)	RR 0.42 (0.12 to 1.49)	59 fewer per 1000 (from 90 fewer to 50 more)	VERY LOW

SFJ=Sapheno-femoral junction; GSV=Great saphenous vein; SSV=Small saphenous vein; DVT=Deep vein thrombosis

(a) Outcomes were downgraded by two levels for limitations because of at least two of the following: lack of allocation concealment, lack of blinding and poor methods to control for attrition bias.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

7.2.1.1 Narrative summary (for outcomes not appropriate for GRADE)

Quality of life

Blomgren 2006A[8] reported that there were no significant differences between the groups for any SF-36 domain at 1 or 2 years. No other data were given.

Blomgren 2011[9] reported that there were no significant differences between the groups for any SF-36 domain at 7 years. No other data were given.

Smith 2002[96]: reported means of AVVQ score at 6 weeks (but no variance measures) of 10.85 for the duplex group and 15.85 for the non-duplex group (p=0.034) [higher score denotes worse outcome]. No difference between the groups were reported at 12 months (p=0.187); data were given in a low-resolution figure, not in the text. SF-36 was reported to be similar across groups at 6 weeks (p>0.38) or 12 months (p>0.15).

7.2.2 Economic evidence

Published literature

One study was included with the relevant comparison.[10] This is summarised in the economic evidence profile below (Table 57). See also the study evidence table in appendix H.

Table 44: Economic evidence profile: pre-operative duplex ultrasound verses no pre-operative duplex ultrasound

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Blomgren 2006[10] (Sweden)	Partially applicable[a]	Potentially serious limitations[b]	Investigation into the effect that use of duplex in assessment has on the cost of varicose vein treatment over a two year horizon.	£128	No significant difference in quality of life between groups (no other data given)[8]	Not reported	Not reported

(a) The study was carried out from a Swedish care-giver perspective, thus applicability to the UK NHS is limited. Costs are discounted at 3% rather than at 3.5% as used in the NICE reference case. QALYs are not calculated.

(b) The time horizon was restricted to two years and thus may not fully capture cost differences between the different assessment strategies; specifically, costs of re-treatment post 2 years which are likely to favour use of duplex will not have been captured. Uncertainty is not formally explored, but the authors note that with a longer follow-up the use of duplex could be cost-saving.

7.2.3 Evidence statements

7.2.3.1 Clinical

Patient assessed symptoms

- *2 year follow-up:* 1 study comprising 250 participants' legs showed that duplex prior to treatment was associated with a lower number of reports of unchanged or worse operated legs at 2 years compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *7 year follow-up:* 1 study comprising 231 participants' legs showed that duplex prior to treatment was associated with a lower number of reports of unchanged or worse operated legs at 7 years compared to no duplex. However this was not a large enough effect to show a clearly appreciable clinical benefit of using duplex [VERY LOW QUALITY].

SFJ reflux

- *6-8 week follow-up:* 2 studies comprising 515 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SFJ reflux at 6-8 weeks compared to no duplex. This was a large enough effect to show a clearly appreciable clinical benefit of using duplex [LOW QUALITY].
- *2 year follow-up:* 1 study comprising 256 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SFJ reflux at 2 years compared to no duplex. This was a large enough effect to show a clearly appreciable clinical benefit of using duplex [LOW QUALITY].
- *7 year follow-up:* 1 study comprising 194 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SFJ reflux at 7 years compared to no duplex. This was a large enough effect to show a clearly appreciable clinical benefit of using duplex [LOW QUALITY].

SPJ reflux

- *6-8 week follow-up:* 1 study comprising 326 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SPJ reflux at 6-8 weeks compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *2 year follow-up:* 1 study comprising 256 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SPJ reflux at 2 years compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *7 year follow-up:* 1 study comprising 194 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SPJ reflux at 7 years compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

GSV reflux at 1 year

- 1 study comprising 189 participants' legs showed that duplex prior to treatment and no duplex did not differ with respect to GSV reflux at 1 year [VERY LOW QUALITY].

SSV reflux

- *6 week follow-up:* 1 study comprising 189 participants' legs showed that duplex prior to treatment was associated with a lower incidence of SSV reflux at 6 weeks compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

- *1 year follow-up:* 1 study comprising 189 participants' legs showed that duplex prior to treatment was associated with a slightly lower incidence of SSV reflux at 1 year compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Perforators reflux at 6 weeks

- *6 week follow-up:* 1 study comprising 189 participants' legs showed that duplex prior to treatment was associated with a lower incidence of perforators reflux at 6 weeks compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *1 year follow-up:* 1 study comprising 189 participants' legs showed that duplex prior to treatment was associated with a lower incidence of perforators reflux at 1 year compared to no duplex. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using duplex [VERY LOW QUALITY].

Development of new branch varicosities at 1 year

- 1 study comprising 189 participants' legs showed that duplex prior to treatment and no duplex did not differ with respect to development of new branch varicosities at one year [VERY LOW QUALITY].

Need for, or actual, re-operation

- *2 year follow-up:* 1 study comprising 292 participants' legs showed that duplex prior to treatment was associated with a lower incidence of reoperation at 2 years compared to no duplex. This was a large enough effect to show a clearly appreciable clinical benefit of using duplex [LOW QUALITY].
- *7 year follow-up:* 1 study comprising 258 participants' legs showed that duplex prior to treatment was associated with a lower incidence of reoperation at 7 years compared to no duplex. This was a large enough effect to show a clearly appreciable clinical benefit of using duplex [LOW QUALITY].

Adverse events –DVT at 2 years

- 1 study comprising 292 participants' legs did not report any DVT events in either group at 2 years, so relative benefit or harm was not estimable [LOW QUALITY].

Venous ulcer at 7 years

- 1 study comprising 158 participants' legs did not report any venous ulcers at 7 years after operation, so relative benefit or harm was not estimable [LOW QUALITY].

Pigmentation/eczema at 7 years

- 1 study comprising 158 participants' legs showed that duplex prior to treatment was associated with a lower incidence of pigmentation or eczema at 7 years compared to no duplex, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

7.2.3.2 Economic

- One cost-comparison study was identified which found that the use of duplex in pre-operative assessment increased the costs of varicose vein treatment; QALYs were not considered, and no incremental analysis was provided.

7.3 Recommendations and link to evidence

Recommendation	8. Consider using duplex ultrasound to confirm the diagnosis and to plan treatment for people with suspected primary or recurrent varicose veins.
Relative values of different outcomes	When reviewing the studies assessing the diagnostic accuracy of hand held Doppler ultrasound as a proxy to the gold standard of duplex, the outcome was diagnostic accuracy, quantified in terms of sensitivity and specificity. The GDG viewed that a false negative result was more important than a false positive result as failing to detect reflux is potentially more harmful than falsely detecting reflux as failure to detect reflux could lead to progression of disease. Sensitivity was therefore considered more important than specificity. For the question concerning the impact of duplex assessment prior to treatment the GDG considered that patient assessed outcomes (quality of life and "operated legs unchanged or worse") were the most important. This was followed, in decreasing order of importance, by the need for further treatment / recurrence, the development of complications, reflux and adverse events.
Trade off between clinical benefits and harms	Clear, clinically important benefits were demonstrated when duplex was used for preoperative assessment in terms of both the patient perception of the state of operated legs (identified as one of the most important outcomes) and the reduced need for reoperation at 7 years. Short term benefits were seen at 6 weeks using the AVVQ but there were no clear long-term benefits in terms of quality of life as measured by SF-36. There were no detected clinical harms from completing a duplex ultrasound assessment prior to treatment. A clear, clinically important beneficial effect on reflux was demonstrated at the sapheno-femoral junction at all time-points, Effects in the sapheno-popliteal junction, GSV and SSV were uncertain at all time-points. The diagnostic studies showed hand held Doppler ultrasound did not have uniformly good diagnostic accuracy across all veins compared with the gold standard of duplex ultrasound. The GDG agreed that the evidence demonstrated that hand held Doppler was not a good substitute for duplex as the levels of incorrect reflux assessment were unacceptable. Up to 20% of people with reflux at the saphenous popliteal junction and 60% of those with reflux in the popliteal vein would not be diagnosed using a hand held Doppler. The GDG agreed that it was important to get a full assessment of the venous haemodynamics of the entire lower limb prior to interventional procedures in order to provide effective treatment, and that the superficial veins should not be treated unless the deep veins had been adequately assessed.
Economic considerations	One cost-comparison study was identified which found that the use of duplex in pre-operative assessment. This study was considered to have severe limitations with the short time horizon (2 years) likely to bias against the use of duplex in pre-operative assessment. The study concluded that duplex would increase the costs of varicose vein treatment in the first two years post-assessment. QALYs were not considered and no incremental analysis was provided. The clinical evidence showed clinically important benefits for duplex in terms of the need for/actual reoperation at 7 years. Therefore when considering a longer time-horizon, the GDG strongly felt that the use of duplex may be cost saving. No published economic evidence was available for the comparison of hand held Doppler compared with duplex ultrasound for the assessment of venous reflux in the legs. It was not possible to obtain unit costs for the two techniques but the GDG felt that the use of duplex ultrasound was likely to be more expensive than hand held Doppler in the short term. However, the use of duplex would substantially improve the quality of treatment, leading to fewer retreatments and scans in the future, and therefore may save cost in the long term. The GDG agreed that the clinical benefit of using duplex, along with the potential long term cost savings, would outweigh the

	extra cost of the initial duplex scan.
Quality of evidence	Four RCTs were identified for review question about the use of duplex prior to treatment. These studies were graded as very low, largely due to serious limitations (such as lack of allocation concealment or lack of blinding). Twelve diagnostic studies were identified and the quality of evidence varied from moderate to very low. The major limitations were a lack of blinding, poor reporting of the duration between tests, and unclear levels of tester competence. Furthermore, single studies sometimes used different thresholds for the reference and index tests with reflux of >0.5 seconds or >1 second being used.
Other considerations	The GDG were unanimous in their agreement that duplex ultrasound should be completed prior to interventional treatment. They noted that duplex ultrasound describes an optimal level of information acquisition in both the deep and superficial venous system and can be standardised. Duplex ultrasound provides accurate anatomical and haemodynamic information and establishes different anatomical patterns of the venous system and can measure flow haemodynamic and vein diameters, upon which better clinical decisions are made. The recommendation in section 9.7 states that endothermal ablation should be offered to patients with symptomatic truncal reflux. If the patient is not suitable for endothermal ablation, foam sclerotherapy should be offered, and if both endothermal ablation and ultrasound-guided foam sclerotherapy are unsuitable, surgery should be offered. This recommendation was based on the results from the economic model. The GDG agreed that it was not possible to assess suitability for this hierarchy of treatment (let alone the need for, and appropriateness, of any treatment) without duplex ultrasound. The GDG agreed that the evidence reviewed supported their clinical experience that clinical examination and the use of hand held Doppler alone is insufficient for the exploration of the deep and superficial venous anatomy. This assessment cannot rule out a potential deep venous thrombosis or a venous malformation. In their expertise they noted huge anatomical variations in the superficial venous system, especially in the region of the popliteal fossa, bifid great saphenous veins and extra-fascial location of the great saphenous veins, which might contraindicate endovenous thermal ablation. The source of reflux in the great saphenous vein can have a variety of presentations, such as vulvar vein in the case of pelvic congestion syndrome, an incompetent thigh perforator or in the case of small saphenous vein, an absent junction, the presence of an ascending pathological reflux through the Giacomini vein, incompetent perforator of the popliteal fossa and a highly located sapheno-popliteal junction. More important, duplex ultrasound can provide an insight into the status of the deep venous system and can rule out the presence of thrombosis and an incompetent primary deep venous system. The GDG identified this recommendation as a key priority for implementation as they felt that it would result in a reducing variation in care and outcomes. They also felt that it would have an impact on outcomes important to patients.

1

8 Conservative Management

Graduated compression hosiery is widely used as first line treatment for symptomatic venous hypertension. Compression stockings work by compressing the superficial veins to keep them collapsed and empty of blood and thereby pushing more blood into the deep venous system. This results in a reduction of venous pressure in the leg and subsequently a decrease in leg swelling. The compression is graduated, exerting an external pressure which is higher at the ankle (minimum 14mmHg) than the calf and thigh, thus increasing blood velocity within the deep venous system. It is recognised that the amount of pressure required is dependent on the severity of the condition.

There are many different makes and types of graduated compression hosiery available on prescription and to buy. These include different lengths (knee or thigh length) and different compression strengths. Confusingly, the British and European standards for classifying the strength of compression hosiery differ and are presented below (Table 45). Class III may be more effective, but consideration should be given to the manual dexterity of the person as they are more difficult to put on. The most frequently prescribed graduated compression hosiery for symptoms of venous hypertension is European standard class II. Adherence with hosiery is an important consideration as the effectiveness of this treatment is dependent on it being worn.

Table 45: Comparison of compression hosiery standards

Class of Stocking	British Standard (mmHg)	European/RAL standard (mmHg)
I	14-17	18-21
II	18-24	23-32
III	25-35	34-46

Alongside compression therapy, general health advice about exercise and weight loss has been proposed as a way of reducing severity of symptoms and prevention of the progression of varicose veins. Elevation of the legs above the level of the heart when sitting down has also been suggested as useful in alleviating symptoms.

This chapter aims to answer two questions:

1. The efficacy and cost effectiveness of compression therapy versus no treatment or lifestyle advice.
2. The efficacy and cost effectiveness of compression therapy versus interventional treatment (foam sclerotherapy, endothermal ablation or surgery).

8.1 Review question: What is the clinical and cost effectiveness of compression therapy compared with no treatment or lifestyle advice in people with leg varicose veins?

For full details see review protocol in appendix C.

Table 46: PICO characteristics of review question

Population	Adults with varicose veins in the legs
Intervention/s	Compression therapy, specifically compression hosiery (compression stockings). Both above knee and below knee compression hosiery will be included. [There will be no comparison between types or intensities of compression therapy].
Comparison/s	• No treatment, or • non compressive stocking, or • placebo, or • lifestyle advice (including advice on weight loss, exercise, smoking, occupational standing/leg elevation etc.).

Outcomes	• Patient reported outcomes
	  ○ Health-related quality of life.
	  ○ Patient assessed symptoms
	• Physician-reported outcomes
	• Need for additional/further treatment
	• Adverse events from intervention
	• Prevention of complications from varicose veins

Study design	Randomised control trials and observational studies

8.1.1 Clinical Evidence

We searched for randomised control trials comparing the effectiveness of compression treatment to no treatment as an intervention for varicose veins. Three studies were included in this review. Two were cross-over trials [3,4] and one was a parallel trial [49].

Comparators were no treatment [49], a non-compressive stocking [4] and a non-specified placebo [3]. The only outcomes covered by these studies were patient-reported symptoms and adverse events.

Because of the paucity of RCT evidence an additional search for observational studies was conducted. Five studies were found. Three were prospective single group studies observing the effects of compression applied as an intervention [45,54,61]. These did not fully match the review question, because as single group studies they could not compare compression to no treatment or lifestyle advice, and were instead before-after designs. However, since the pre-compression stage could be regarded as equivalent to no treatment, it was deemed acceptable to consider the evidence from these reports, despite the high threats to internal validity, such as time or placebo effects, inherent in a before-after design. Two additional studies were retrospective surveys of previous and present compression therapy use [75,81], where compression was not applied as part of the study. All observational study data have been analysed in a narrative form (section 8.1.1.1.2).

Summary of included studies

Information on the populations, interventions and outcomes used in all 8 studies are summarised in Table 47and Table 48. See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

1 **Table 47: Summary of the RCTs included in the review**

Study	Design	Patient group	Compression treatment	Outcomes
Benigni 2003[4]	Cross over RCT (but most results relevant to this review were only presented for the first phase, before cross-over). N=125 Follow-up 14 days	Females; 18-75 years; early stage chronic venous disease (CVD), but competent deep venous trunks.	13-20 hPa (9.8-15.0 mmHg) Class 1 knee-high graduated compression stockings.	Patient assessed symptoms Adverse events
Anderson 1990[3]	Cross over RCT. N=72; Follow-up 50 days including 28 days treatment period	Males and females; 20-61 years; on waiting list for varicose vein surgery.	Full length hosiery fitted to give a pressure of 30-40mmHg. To be removed in bed.	Patient assessed symptoms
Krijnen 1997[49]	Parallel group RCT (quasi-randomised). N=114; Follow-up 3 months	Male factory workers with a predominantly standing job. All had clinical evidence of chronic venous insufficiency (CVI) but no ulceration. No demographic details given.	Below knee class II (30-32mmHg) seamless compression stockings, to only be used during working hours.	Patient assessed symptoms Adverse events

2

3 **Table 48: Summary of the observational studies included in the review**

Study	Design	Patient group	Compression treatment	Outcomes
Motykie1999[61]	Observational single group before and after study. N=112 Follow-up: 1 and 16 months	Patients with chronic venous incompetence (CVI).	30-40 mmHg compression stockings for 16 months. Hours per day and night use unclear. 36% thigh length, 17% mid-thigh and 47% knee or calf length	Patient assessed symptoms Adverse events
Junger1996[45]	Observational single group before and after study. N=20 Follow-up: 2 and 4 weeks	CVI class I and II.	2 weeks of short stretch bandaging, followed by 2 weeks with class II compression stockings.	Patient assessed symptoms
Lurie2011[54]	Observational single group before and after study. N=121 Follow-up: 2-6	Patients with primary chronic venous disease (CVD).	20-30mmHg knee-high compression stockings for 2-6 weeks, with lifestyle advice as	Disease specific quality of life Patient assessed symptoms

Study	Design	Patient group	Compression treatment	Outcomes
	weeks		well (weight loss, exercise and frequent leg elevation).	
Pannier2007[75]	Cross-sectional questionnaire/interview study. N=961	Population with C2-C6, taken from a random population of 3072.	Those with a history of varicose veins were asked about their use of compression stockings	Patient assessed symptoms Adverse events Compliance
Raju2007[81]	Observational case series.	New CVD cases, CEAP classes C2-6.	Those who had been prescribed compression stockings in the past were asked about their compliance and reasons for non-use.	Compliance

1

Table 49: Clinical evidence profile (GRADE table): compression versus no treatment (RCT studies only)

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Compression Frequency (%) OR mean (sd) [n]	control Frequency (%) OR mean (sd) [n]	Relative Risk (95% CI)	Absolute effect, mean difference or standardised mean difference* (95% CI)	
Numbers of patients with pain or no improvement in pain at end of treatment										
2 Benigni 2003[4] Krijnen 1997[49]	randomised trials	very serious[a]	Serious[b]	no serious indirectness	no serious imprecision	29/91 (31.9%)	49/87 (56.3%) median control risk: 52.6%	Random effects RR 0.41 (0.12 to 1.4)	310 fewer per 1000 (from 463 fewer to 210 more	VERY LOW
Pain levels (VAS) at end of treatment (Better indicated by lower values). Different VAS scales (one was probably calculated out of 10 and the other probably calculated out of 100) were probably used, so standard mean difference has been used)										
2 Anderson 1990[3] Benigni 2003[4]	randomised trials	very serious[a]	very serious[b]	no serious indirectness	Serious[c]	34.7 (29.25) [66] 1.4(1.8) [62]	37.6(29.25)[66] 2.9(2.1)[55]	-	Random effects SMD 0.43 lower (1.08 lower to 0.23 higher)	VERY LOW
Numbers of patients with heavy or tired legs or no improvement in heavy or tired legs at end of treatment										
2 Benigni 2003[4] Krijnen 1997[49]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	28/89 (31.5%)	53/88 (60.2%) median control risk: 58.9%	RR 0.52 (0.36 to 0.73)	283 fewer per 1000 (from 159 fewer to 377 fewer)	LOW
Heavy or tired legs level (VAS 0–100) at end of treatment (Better indicated by lower values										
1 Anderson 1990[3]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	34.1(30.9) [66]	36.3(28.4)[66]	-	MD 2.2 lower (12.33 lower to 7.93 higher)	LOW

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Compression Frequency (%) OR mean (sd) [n]	control Frequency (%) OR mean (sd) [n]	Relative Risk (95% CI)	Absolute effect, mean difference or standardised mean difference* (95% CI)	
Numbers of patients with no improvement in cramps at end of treatment										
1 Benigni 2003[4]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness[B]	Serious[c]	37/61 (60.7%)	44/55 (80%)	RR 0.76 (0.6 to 0.97)	192 fewer per 1000 (from 24 fewer to 320 fewer)	VERY LOW
Night cramps level (VAS 0–100) at end of treatment (Better indicated by lower values)										
1 Anderson 1990[3]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	22.4(25.2) [66]	24.9(24.4)[66]	-	MD 2.5 lower (10.96 lower to 5.96 higher)	LOW
Numbers of patients reporting no improvement in ankle swelling at end of treatment										
1 Benigni 2003[4]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	35/61 (57.4%)	43/53 (81.1%)	RR 0.71 (0.55 to 0.91)	235 fewer per 1000 (from 73 fewer to 365 fewer)	VERY LOW
Self-reported swelling levels (VAS 0–100) at end of treatment (Better indicated by lower values)										
1 Anderson 1990[3]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	28.2(29.25) [66]	35.3(30.1)[66]	-	MD 7.1 lower (17.23 lower to 3.03 higher)	VERY LOW
Body image dissatisfaction (VAS 0–100) at end of treatment (Better indicated by lower values)										

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Compression Frequency (%) OR mean (sd) [n]	control Frequency (%) OR mean (sd) [n]	Relative Risk (95% CI)	Absolute effect, mean difference or standardised mean difference* (95% CI)	
1 Anderson 1990[3]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	43.2(7.4) [66]	41.1(38.2)[66]	-	MD 2.1 higher (10.8 lower to 15 higher)	LOW
Numbers of patients with decrease in complaints by the end of treatment										
1 Krijnen 1997[49] Mark	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	17/30 (56.7%)	4/34 (11.8%)	RR 4.82 (1.82 to 12.73)	449 more per 1000 (from 96 more to 1380 more)	LOW

VAS =visual analogue scale; SMD = standard mean difference; MD = mean difference; RR = relative risk

** Standard mean differences are used whenever scores from different measurement scales are combined.*

(a) All outcomes from all studies had at least 2 of the following serious limitations: unclear allocation concealment, unclear blinding, inadequate reporting of baseline values and a lack of ITT.

(b) For those outcomes where inconsistencies could not be explained by pre-specified sub-grouping downgrading was as follows: if I squared was between 50% and 75% the outcome was downgraded to serious limitations; if I squared was >75% the outcome was downgraded to very serious limitations. A random effects model was then applied.

(c) If the confidence interval of the effect ranged from no effects to either appreciable benefit or harm imprecision was downgraded once, whereas if the confidence interval ranged from appreciable benefit to appreciable harm imprecision was downgraded twice.

8.1.1.1 Narrative summary

8.1.1.1.1 RCT (for outcomes that are not appropriate for GRADE due to incomplete outcome reporting)

Minor adverse events

Benigni, 2003 [4] reported a significant difference, favouring the compression group, of minor adverse events (a slipping sensation, a warming sensation or a feeling of pressure) between the compression and control groups at the end of the full cross-over trial. No statistics were provided.

Compliance

Benigni , 2003 [4] reported compliance as not significantly different between groups, without group statistics being given.

Krijnen, 1997 [49] asked 15 participants who had been given stockings but who hadn't worn them every day (and thus been excluded from results for other outcomes) for the predominant single reason for their non-compliance. Five felt that the stockings were too tight, two stated they suffered from red and swollen skin, two stated that the stockings kept sliding down, and two reported an itch. Other reasons given did not relate to adverse effects.

8.1.1.1.2 Observational studies

Disease Specific Quality of life (score ranges from 0-190, with 190 being the worst score).

Lurie, 2011[54] reported an improvement in the specific quality of life and outcome response – venous (SQOR-V) scale from a mean (sd) 62.5(20.6) pre-compression to 48.9(17.9) post compression.

The GRADE-equivalent rating for this evidence is VERY LOW, due to the inherently high risks of bias in observational research.

Patient assessed symptoms

Motykie, 1999 [61] reported a significant improvement in all symptom outcomes between baseline and one month, and also baseline and 16 months (Table 50).

Table 50: Symptom outcomes in the Motykie1999[61] study

Patient assessed symptoms[a] (1-5 scale, with 1=minimal problem and 5=maximal problem)	**pre-compression mean (sd)** n=112	**1 month post-compression mean (sd)** n=112	**16 months post-compression mean (sd)** n=112	**p value** (Wilcoxon signed ranks test used)
swelling	2.45(1.25)	1.47(0.83)	1.13(0.51)	P<0.001 for comparison between baseline and 1 month for all variables. P<0.0001 for comparison between baseline and 16 months for all variables.
pain	2.94(1.29)	1.77(1.09)	1.38(0.69)	
discolouration	2.76(1.29)	2.23(1.22)	1.81(0.99)	
cosmetic problems	3.03(1.41)	2.50(1.41)	1.98(0.99)	
activity tolerance	2.33(1.35)	1.71(1.19)	1.38(0.73)	
depression	1.72(1.12)	1.42(0.87)	1.29(0.81)	
sleep problems	2.00(1.25)	1.46(0.99)	1.24(0.63)	

Junger, 1996 [45] reported that subjective treatments in all patients decreased during treatment, except for a feeling of "coldness", which increased. There were no complaints by patients about feelings of constriction. No numerical data were presented.

Lurie, 2011[54] reported an improvement in a symptom score from mean (sd) 16.9(9.8) pre-compression to 6.3(5.8) post compression. This was generated by part of the SQOR-V form, comprising severity of pain, heaviness, itching, night cramps, heat or burning, tingling, throbbing, restless legs, swelling. The symptom score was the sum of the scores of these 9 symptoms, each on a 6 point scale; a higher score indicated worse symptoms, with 54 the worst score.

Pannier, 2007 [75] reported that 71.3% of the interviewed participants using compression said their medical condition had improved with compression therapy. This included:

- reduction in swelling (84.2%)
- reduction in heaviness (89.4%)
- reduction in leg pain after prolonged standing (60.9%)
- reduction in tension in the legs (78.9%)

The GRADE-equivalent rating for this evidence is VERY LOW, due to the inherently high risks of bias in observational research.

Minor adverse events

Motykie, 1999 [61] reported that adverse events of numbness, sweating, itchiness and new pain existed after compression treatment. However these adverse events were mild (all scored as <1.5/5 on a scale where 5 is the worst possible), and improved as therapy progressed from 1 month to 16 months.

Pannier 2007[75] reported the following adverse events:

- pruritis (8.4%)
- eczemas (1.6%)
- constrictions under compression therapy (8.4%)
- slipping of stockings (3.6%)

The GRADE-equivalent rating for this evidence is VERY LOW, due to the inherently high risks of bias in observational research.

Compliance

Motykie, 1999 [61] reported that 92/112 (82%) were still wearing stockings at 1 month and 78/112 (69.6%) were still wearing stockings at 16 months.

Raju, 2007 [81] reported that out of the patients who had been prescribed stockings, full compliance (daily use) was reported by 28%, full and partial (most days use) compliance by 44% and full, partial and minimal (occasional use) compliance by 49.33%. Primary reasons for non-use of stocking, of those that were recommended stockings by their doctor are given in Table 51, were:

Table 51: Primary reasons for non-use of stocking

Reason for non-compliance	Percentage of patients reporting reason
unable to state a reason	40%
lack of efficacy	20%
poor fit/cut off circulation	17.3%
too hot	9.3%

Reason for non-compliance	Percentage of patients reporting reason
soreness	2.7%
needs application assistance	2.7%
cosmetic reasons	2.7%
itching/dermatitis	2.7%
worsening of symptoms	1.3%
lack of self- discipline	0.7%
cost	0.5%
work-related	0.3%

The GRADE-equivalent rating for this evidence is VERY LOW, due to the inherently high risks of bias in observational research.

8.1.2 Economic evidence

8.1.2.1 Literature review

No cost effectiveness evidence was identified for this question.

8.1.2.2 Unit costs

In the absence of recent UK cost effectiveness evidence, unit costs are provided in Table 52 and Table 53 to aid consideration of the cost effectiveness of compression hosiery compared to no treatment.

Table 52: Types of compression hosiery and unit costs

Item	Cost			
	Standard compression stockings		Made-to-measure compression stockings	
	Below-knee	Thigh-high	Below-knee	Thigh-high
Class I compression stockings	£7.21	£7.89	£26.46	£42.30
Class II compression stockings	£10.54	£11.73	£26.46	£42.30
Class III compression stockings	£11.95	£13.90	£26.46	£42.30

Source: NHS Drug tariff [70]

Table 53: Unit costs and quantity of the components of compression therapy

Item	Unit cost	Quantity per year	Notes
Practice nurse time	£43	1.5 hours	Per hour cost of practice nurse patient contact time
Compression stockings/hosiery	£42	4	Price of a pair of thigh-high "made-to-measure" compression stockings. The same price applies to class I, class II and class III compression stockings.

Source: NHS Drug tariff[70]*,PSSRU*

8.1.2.3 Economic considerations

Based on the figures provided in Table 53, it is estimated that the annual costs of compression hosiery would be approximately £234. This estimate is based on the assumption that compression

stockings have a life expectancy of 3 months, after which they lose their strength. Patients are given two pairs of "made-to-measure" thigh-high stockings for use over a six month period. The cost of lifestyle advice was assumed negligible.

In practice, some people may be prescribed below-knee standard compression stockings instead of thigh-high "made-to-measure" stocking. If below-knee standard compression stockings are prescribed it is estimated (assuming the average price of a pair of standard below-knee compression stockings is £10.54) that the annual costs of compression therapy would be roughly £107.

Assuming the difference in costs of compression hosiery and the no-treatment option is £234, compression hosiery will be cost-effective at the £20,000 per QALY threshold if it provides an improvement of 0.012 quality-adjusted life years (QALYs) relative to no treatment. If the difference in the costs of compression hosiery and no-treatment option is £107, compression hosiery will be cost-effective if it provides an improvement of 0.005 QALYs relative to no treatment or lifestyle advice.

The unknown in this analysis is whether compression therapy will offer an improvement of 0.012 (0.005) QALYs relative to no treatment or lifestyle advice. The review of the clinical effectiveness evidence on compression versus no treatment (lifestyle advice) did not report any single measure of health-related quality of life, however it did show that compression hosiery is more effective (Table 49) than no treatment. For example, the number of people reporting heavy or tired legs was found to be lower with compression (risk ratio of 0.52 [95% CI: 0.36 – 0.73]), and the number of people with a decrease in complaints at the end of treatment was greater for compression (risk ratio of 4.82 [95% CI: 1.82 – 12.73]), compared to no-treatment or lifestyle advice. Compression was also more effective than no-treatment in reducing the number of people with cramps and ankle swelling.

8.1.2.4 New cost-effectiveness analysis

New analysis was not prioritised for this question.

8.1.3 Evidence statements

8.1.3.1 Clinical

8.1.3.1.1 RCT studies only

Patient reported symptoms

Patient reported pain

- 2 studies comprising 178 participants found that compression led to a relative reduction in the rates of **patients experiencing pain / no improvement in pain**, but the uncertainty of this effect is too large from which to draw clear conclusions regarding benefits or harms [VERY LOW QUALITY].
- 2 studies comprising 249 participants found that compression led to a relative reduction in the **level of pain**, but the uncertainty of this effect is too large from which to draw clear conclusions regarding benefits or harms [VERY LOW QUALITY].

Patient reported heavy or tired legs

- 2 studies comprising 177 participants found that compression was associated with relatively lower rates of **patients experiencing heavy or tired legs / no improvement in heavy or tired legs**. This was a large enough effect to show a clearly appreciable clinical benefit of using compression stockings [LOW QUALITY].
- 1 study comprising 132 participants found that compression led to a relative reduction in the **level of heavy or tired legs**, but the uncertainty of this effect is too large from which to draw clear conclusions regarding benefits or harms [LOW QUALITY].

Patient reported cramps

- 1 study comprising 116 participants found that compression was associated with relatively lower rates of **patients experiencing no improvement in cramps**. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using compression stockings [VERY LOW QUALITY].
- 1 study comprising 132 participants found that compression led to a relative reduction in the **level of night cramps**, but the uncertainty of this effect is far too large from which to draw clear conclusions regarding benefits or harms [LOW QUALITY].

Patient reported swelling

- 1 study comprising 114 participants found that compression was associated with relatively lower rates of **patients experiencing no improvement in swelling**. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using compression stockings [VERY LOW QUALITY].
- 1 study comprising 132 participants found that compression led to a relative reduction in the **level of ankle swelling,** but the uncertainty of this effect is too large from which to draw clear conclusions regarding benefits or harms [VERY LOW QUALITY].

Patient reported body image dissatisfaction

- 1 study comprising 132 participants found that compression led to a relative reduction in the level of **body image dissatisfaction** but the uncertainty of this effect is too large from which to draw clear conclusions regarding benefits or harms [LOW QUALITY].

Overall complaints of symptoms

- 1 study comprising 64 participants found that compression was associated with relatively higher **rates of patients experiencing a reduction in overall complaints**. This was a large enough effect to show clearly appreciable clinical benefit [LOW QUALITY].

8.1.3.1.2 Observational study evidence

Evidence from observational data suggests that compression may improve quality of life and reduce symptoms, but the potential for bias in this evidence is extremely high.

Observational data also suggests that adverse events such as numbness, sweating, itchiness, pain, eczema, constriction and slippage of stockings occur with compression therapy, but that these are mild and infrequent.

Observational compliance was reported as being relatively low, with full compliance at only 28% in one study. Another study reported a higher figure of almost 70% but the level of compliance was unclear, and may have included very occasional use.

8.1.3.2 Economic

No cost effectiveness evidence was found for this question. The annual cost of compression therapy was estimated to be £107-£234.

8.2 Review questions: What is the clinical and cost effectiveness of compression therapy compared with a) stripping surgery; or b) endothermal ablation; or c) foam sclerotherapy in people with leg varicose veins?

For full details see review protocol in appendix C.

Table 54: PICO characteristics of review question

Population	Adults with varicose veins in the legs
Intervention/s	Compression therapy, specifically compression hosiery (compression stockings)
Comparison/s	Foam sclerotherapy crossectomy OR Stripping surgery + ligation [± phlebectomy] OR Endothermal ablation [± foam sclerotherapy/phlebectomy]
Outcomes	• Patient-reported outcomes ○ Health-related quality of life ○ Patient-assessed symptoms • Physician-reported outcomes. • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work/normal activities
Study design	Randomised controlled trials

8.2.1 Clinical evidence

We searched for randomised controlled trials comparing the effectiveness of compression therapy and interventional therapies such as foam sclerotherapy, stripping surgery or endothermal ablation for improving outcomes for varicose veins.

Summary of included studies

No RCTs were found comparing compression to either foam sclerotherapy or endothermal ablation.

Two RCTs were found comparing compression therapy to stripping surgery [59] [58]. Note that all the data contained in Michaels 2006[58] were also found in Michaels 2006[59], the latter being an HTA report comprising 2 randomised controlled trials relevant to this review question.

Because of the paucity of RCT evidence an additional search for observational studies was conducted. None were identified.

The summary of the included study can be seen in Table 55. See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 55: Summary of studies included in the review

Study	No. of patients	Majority CEAP grade	Age (mean)	Compression details	Type of intervention	Follow-up
Michaels 2006A[58] Also presented in: Michaels 2006[59]	246	Not stated, but had detectable reflux	49	Compression hosiery given alongside lifestyle advice relating to exercise, leg elevation and weight/diet management. Type and pressure of stocking, and duration of treatment, are not reported	Stripping surgery with ligation. Done under general anaesthetic and usually as a day case	24 months

Table 56: Clinical evidence profile (GRADE table): compression versus surgery for varicose veins.

Quality assessment							Summary of findings				
							Event rate (%) / mean (sd) [n]		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Compression	Surgery	Relative (95% CI)	Absolute	
Quality of life (QoL) – SF-6D 1 year (Better indicated by lower values)											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	0.73 (0.11) [98]	0.77 (0.1) [75]	-	MD 0.04 lower (0.07 to 0.01 lower)	LOW
QoL – SF-6D 2 years (Better indicated by lower values)											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	0.72(0.13)[47]	0.78(0.1)[44]	-	MD 0.06 lower (0.11 to 0.01 lower)	LOW
QoL – EQ-5D 1 year (Better indicated by lower values)											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	0.78(0.18)[101]	0.87(0.14)[78]	-	MD 0.09 lower (0.14 to 0.04 lower)	LOW
QoL – EQ-5D 2 years (Better indicated by lower values)											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.85(0.17)[44]	0.84(0.21)[34]	-	MD 0.01 higher (0.08 lower to 0.1 higher)	MODERATE
Patient assessed symptoms (proportion same or worse) – aching at 1 year											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/97 (74.2%)	15/75 (20%)	RR 3.71 (2.33 to 5.92)	542 more per 1000 (from 266 more to 984 more)	MODERATE

Quality assessment							Summary of findings				
							Event rate (%) / mean (sd) [n]		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Compression	Surgery	Relative (95% CI)	Absolute	
Patient assessed symptoms (proportion same or worse) – heaviness at 1 year											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/97 (53.6%)	9/75 (12%)	RR 4.47 (2.36 to 8.47)	416 more per 1000 (from 163 more to 896 more)	MODERATE
Patient assessed symptoms (proportion same or worse) – itching at 1 year											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/97 (43.3%)	10/75 (13.3%)	RR 3.25 (1.75 to 6.04)	300 more per 1000 (from 100 more to 672 more)	MODERATE
Patient assessed symptoms (proportion same or worse) – swelling at 1 year											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/97 (32%)	8/75 (10.7%)	RR 3 (1.46 to 6.13)	213 more per 1000 (from 49 more to 547 more)	MODERATE
Patient assessed symptoms (proportion same or worse) – body image concerns at 1 year											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/97 (77.3%)	13/75 (17.3%)	RR 4.46 (2.69 to 7.4)	600 more per 1000 (from 293 more to 1000 more)	MODERATE
Adverse events - neural damage (foot drop)											
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/122 (0%)	1/124(0.8%)	RR 0.34 (0.01 to 8.24)	5 fewer per 1000 (from 8 fewer to 58 more)	VERY LOW
Patient dissatisfaction at 1 year											

Quality assessment							Summary of findings				
							Event rate (%) / mean (sd) [n]		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Compression	Surgery	Relative (95% CI)	Absolute	
1 Michaels 2006A[59]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/107 (49.5%)	3/65 (4.6%)	RR 10.73 (3.5 to 32.94)	449 more per 1000 (from 115 more to 1000 more)	MODERATE

(a) Outcomes were downgraded by one level for limitations because of a lack of any blinding in the study.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

8.2.2 Economic evidence

8.2.2.1 Literature review

Three studies[36,59,86] were included that included the relevant comparisons. These are summarised in the economic evidence profile below (Table 57). See also the study selection flow chart in appendix E and study evidence tables in appendix H.

One study[30] was excluded. The excluded study is summarised in appendix K, with reasons for exclusion given.

8.2.2.2 New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis, in which compression hosiery was compared to various interventional treatments. Results are summarised in the economic evidence profile below (Table 57). Full details can be found in appendix L, and a summary in section 9.6.

Table 57: Economic evidence profile: Compression hosiery

Study	Applicability	Limitations	Other comments	Comparators	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gohel et al. 2010[36]	Directly applicable	Potentially serious limitations[a]	The study employed a decision analytic model with a 5 year time horizon. A decision tree is used to model the first 3 months, and a Markov model is used to model the remainder of the time horizon, broken down into 3-month cycles. The study focuses on patients with primary varicose veins in one leg (unilateral).	Day case surgery verses conservative care	£1,242	0.429 QALYs	ICER = £2,895 per QALY gained. Day-case surgery was the cost-effective option	Surgery (IP), RFA (LA), RFA (GA), EVLA (GA), EVLA (LA) and UGFS were also found to be cost effective compared to conservative care.[bc] Results are sensitive to the initial costs of surgery, estimates of treatment effectiveness (specifically, the odds ratio for occlusion of the great saphenous vein) and the relative risk of retreating residual varicosities after sequential versus concomitant phlebectomy.[d]
Michaels et al. 2006[59]	Directly applicable	Minor limitations[e]	Cost-effectiveness results are based on a decision-analytic Markov model with a 10-year time horizon to compare sclerotherapy and surgery.	Surgery	£155[f]	0.0439 QALYs[f]	ICER = £3,531 per QALY gained. Surgery is cost effective.	Surgery was also cost-effective compared to conservative care for moderate and severe varicose veins, with ICERs of £3,531 and £1,938 respectively. Cost-effectiveness results fairly robust to sensitivity analyses (ICERs below £20,000 per QALY) conducted on

Study	Applicability	Limitations	Other comments	Comparators	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
								parameters such as probability of residual veins after surgery, progression rate of reflux and the probability and costs of complications after surgery.
Michaels et al. 2006[59] and Ratcliffe et al. 2006[86]	Directly applicable	Minor limitations[g]	Economic analysis based on a randomized controlled trial conducted at two vascular units within the NHS. Patients were allocated randomly to surgical treatment and conservative treatment.	Stripping surgery vs. conservative treatment	£389[h]	0.083 QALYs[h]	£4,687 per QALY gained	Sensitivity analysis showed that the economic results and conclusions are fairly robust. Using EQ-5D values (instead of SF-6D scores) gives an ICER of £3,299 per QALY. Using NHS Reference Costs for surgical treatment (instead of local unit costs) gives an ICER of £5,708 per QALY.
NCGC model	Directly Applicable	Minor limitations[i]	A markov model with one month cycles and a 5 year time horizon was built. The study focused on patients for whom surgery, endothermal treatment, foam sclerotherapy and conservative care were all possible treatments.	Endothermal treatment verses compression hosiery	-£233	0.17 QALYs	Endothermal treatment dominates compression hosiery	Surgery and foam sclerotherapy were also cost effective compared to compression hosiery.[j] Univariate and probabilistic sensitivity analyses were carried out. In none of the investigated scenarios did compression hosiery appear cost effective compared to

Study	Applicability	Limitations	Other comments	Comparators	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
								endothermal treatment. Endothermal had a probability of being cost-effective of 71%, and compression had a probability of being cost-effective of 4%.

(a) Modelling was undertaken over a 5 year time horizon, yet the costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months. All treatments of residual varicosities with ultrasound-guided foam sclerotherapy at 3 months are assumed to be successful.

(b) Surgery-DC refers to day-case surgery, EVLA(LA) refers to endovenous laser ablation performed under local anaesthesia, RFA(LA) refers to radiofrequency ablation performed under local anaesthesia, EVLA(GA) refers to endovenous laser ablation performed under general anaesthesia, Surgery(IP) refers to inpatient surgery and RFA(GA) refers to radiofrequency ablation performed under general anaesthesia

(c) However these interventions were not cost effective compared to each other –day case surgery was the cost-effective option when considering all 8 comparators. Full results are presented in the economic evidence table in appendix H

(d) These results apply to the complete analysis of 8 comparators, rather than to the pairwise comparison of day case surgery compared to conservative care

(e) The retreatment options and rates of retreatment modelled are based on expert opinion, although no detail is given on the expert(s) or how this information was elicited. The clinical pathway is based on strict assumptions of who can receive which treatment, and may not fully reflect what happens in current practice. Utility data is based on an average of SF-36 and EQ-5D data; no reason is provided.

(f) These results apply to minor varicose veins

(g) No decision analytic model was conducted to capture long-term costs and health outcomes. The short 2-year time horizon may underestimate the cost-effectiveness of surgical treatment as the clinical benefits of surgery including improvements in health-related quality of life would be expected to endure beyond 24 months. Including long-term costs and health outcomes may still give lower ICERs.

(h) These results apply to severe varicose veins

(i) Estimated rates of top-up treatment based on GDG estimates, short time horizon of 5 years

(j) However these interventions were not cost effective compared to endothermal treatment. Full results are presented in appendix L

8.2.3 Evidence statements

8.2.3.1 Clinical

8.2.3.1.1 Compression versus surgery

Quality of life

SF-6D

- *1 year follow-up:* 1 study comprising 173 participants showed that surgery was associated with a better quality of life rating at 1 year compared to compression. However this was not a large enough effect to show a clearly appreciable clinical benefit of using surgery [LOW QUALITY].
- *2 year follow-up*: 1 study comprising 91 participants showed that surgery was associated with a better quality of life rating at 2 years compared to compression. However this was not a large enough effect to show a clearly appreciable clinical benefit of using surgery [LOW QUALITY].

EQ 5D

- *I year follow-up:* 1 study comprising 179 participants showed that surgery was associated with a better quality of life rating at 1 year compared to compression. However this was not a large enough effect to show a clearly appreciable clinical benefit of using surgery [LOW QUALITY].
- *2 year follow-up:* 1 study comprising 78 participants showed that surgery and compression did not differ in their effects on quality of life at 2 years [MODERATE QUALITY].

Patient assessed symptoms

Aching at 1 year

- 1 study comprising 172 participants showed that surgery was associated with lower rates of aching at 1 year compared to compression. This was a large enough effect to show a clearly appreciable clinical benefit of using surgery [MODERATE QUALITY].

Heaviness at 1 year

- 1 study comprising 172 participants showed that surgery was associated with lower rates of heaviness at 1 year compared to compression. This was a large enough effect to show a clearly appreciable clinical benefit of using surgery [MODERATE QUALITY].

Itching at 1 year

- 1 study comprising 172 participants showed that surgery was associated with lower rates of itching at 1 year compared to compression. This was a large enough effect to show a clearly appreciable clinical benefit of using surgery [MODERATE QUALITY].

Swelling at 1 year

- 1 study comprising 172 participants showed that surgery was associated with lower rates of swelling at 1 year compared to compression. This was a large enough effect to show a clearly appreciable clinical benefit of using surgery [MODERATE QUALITY].

Body image concerns at 1 year

- 1 study comprising 172 participants showed that surgery was associated with lower rates of body image concerns at 1 year compared to compression. This was a large enough effect to show a clearly appreciable clinical benefit of using surgery [MODERATE QUALITY].

Adverse events –

Neural damage (foot drop)

- 1 study comprising 246 patients showed that surgery was associated with a higher rate of neural damage compared to compression, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Patient reported outcomes

Patient dissatisfaction

- 1 study comprising 172 patients showed that surgery was associated with less patient dissatisfaction than compression. This was a large enough effect to show a clearly appreciable clinical benefit of using surgery [MODERATE QUALITY].

8.2.3.2 Economic

- Three existing cost-utility analyses found surgery to be cost-effective compared to conservative care. These studies were directly applicable, with minor or potentially serious limitations.
- Our original economic analysis also found interventional treatments to be cost-effective compared to conservative care; specifically endothermal treatment was identified as the cost-effective strategy. This evidence is directly applicable with minor limitations.

8.3 Recommendations and link to evidence

The recommendations for this section were made in conjunction with the recommendations for interventional treatment and can be found in section 9.7.

9 Interventional Treatment

Truncal vein treatments

The overwhelming majority of primary varicose veins result from valvular incompetence and subsequent reflux in one of three superficial truncal veins – the great saphenous (GSV), small saphenous (SSV) or the anterior accessory saphenous veins (AASV). These truncal abnormalities are commonly treated by three main methods: stripping surgery, foam sclerotherapy and endothermal ablation.

Stripping surgery

Traditional treatment involves surgical removal by 'stripping'. Stripping the GSV or AASV involves an incision in the groin and disconnection of the sapheno-femoral junction ('crossectomy'). A stripper is then passed down the vein and grasped via a separate incision (often around the level of the knee joint). The stripper is then pulled out and the vein removed. There are many variations on this technique. Similarly, the SSV is stripped via an incision in the popliteal fossa. Stripping is usually performed under general anaesthetic and removal of the varicose tributaries by phlebectomy is often undertaken at the same time.

Foam sclerotherapy

A sclerosant foam (for example, a solution of sodium tetradecyl sulphate mixed with air) is injected into the vein to induce phlebitis and vein occlusion. The foam displaces blood from the vein, creates a massive surface area of sclerosant in contact with the vein endothelium, induces vein spasm and can be seen on ultrasound. Ultrasound-Guided Foam Sclerotherapy (UGFS) can be performed as an out-patient procedure under local anaesthetic. The GDG decided only to include foam sclerotherapy within the guideline as liquid sclerotherapy is not commonly used in current practice.

Endothermal ablation

There are two main endothermal methods: radiofrequency and laser ablation. Like foam sclerotherapy, these methods aims to induce vein occlusion, but they use a thermal rather than a chemical stimulus to the vein lumen. Treatment may be performed under general or local anaesthesia using ultrasound guided puncture of the vein in the lower leg.

A decision was made early in the guideline development process to consider endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) together as one 'endothermal ablation technique', and therefore not review the evidence comparing the techniques. This means the clinical evidence for these techniques has been combined, although subgrouping by technique has been carried out when heterogeneity of effect sizes within meta-analyses has been regarded as excessively high.

There was a great deal of debate about this decision. The GDG noted that the two techniques have developed side by side with incremental technical improvements over the past decade. The basic principle of ultrasound guided endovenous thermal ablation is shared between the techniques and the results are very similar. Many surgeons use both systems favouring one over the other as wavelengths or catheter designs change. A patient who is suitable for treatment with one can usually also be treated by the other.

The GDG noted that in order to compare the two techniques a stringent examination of exact technique used was required. The majority of the GDG felt that there were too many variables within the trials to be able to make meaningful distinctions between the techniques. In contrast, some of the group felt that although both techniques used heat to destroy the veins, they have different

methods of generating power and different side effects. However, on balance, the GDG decided to consider the two techniques together.

The aim of the reviews in section 9.1, 9.2 and 9.3 is to consider the pairwise comparisons to evaluate the optimum treatment(s). The cost effectiveness of these techniques is considered in section 9.6.

Tributary vein treatments

In addition to truncal interventions, treatments directed at incompetent tributaries are also sometimes required. Eradication of varicose vein tributaries has traditionally been performed by surgical removal – also known as 'phlebectomy' or 'avulsions'. The technique has been refined over many years and now involves small, stab incisions and removal of lengths of the vein by traction after extraction with specially designed vein hooks. It is often performed at the same time as treatment for truncal incompetence under general or local ('tumescent') anaesthesia. It may also be performed alone at a later date.

Foam sclerotherapy is an alternative to avulsion surgery for the eradication of varicose tributaries. Foam sclerotherapy of varicose tributaries may be performed alongside endothermal ablation of the truncal vein, or performed alone at a later date.

There is currently little guidance on which of these procedures is more clinically or cost-effective. Section 9.4of the guidance examines the clinical efficacy and cost effectiveness of foam sclerotherapy compared to avulsion therapy for varicose vein tributaries.

Tributary treatment given with truncal treatments versus truncal treatments given alone

There is a degree of controversy with respect to the development of varicose veins and how they should be treated. The majority view, often termed the descending theory, is that reflux begins in the saphenous trunk from where it extends distally into primary and then secondary tributaries, giving rise to reflux in visible varices under the skin. An alternative view, the ascending theory, is that reflux begins in the tributaries themselves from where it extends proximally giving rise to reflux in the main saphenous trunk. These competing concepts suggest that either the tributaries, or alternatively the main saphenous trunk, should be viewed as "innocent bystanders" which do not require direct intervention. If one accepts the descending theory, it might well be reasonable to treat the truncal vein and leave the varices alone in the expectation that the varices will disappear once their cause is eradicated. Alternatively, if one accepts the ascending theory, then it might be reasonable to just deal with the tributary varices in the expectation that the trunk vein will normalise once tributary reflux has been eradicated.

In the UK, although most specialists ascribe to the descending theory, there is controversy as to whether it is necessary to deal with the varices at the same time as eradicating truncal reflux. Thus, some specialists will treat the truncal vein and leave the varices alone in the expectation that they will disappear. Others, possibly the majority, would consider this an incomplete treatment and go on to treat the varices (usually either with stab avulsions or with foam sclerotherapy) at the same time as dealing with the truncal reflux. Section 9.5 of the guideline compares the efficacy and cost effectiveness of these two strategies. There is also a third strategy involving treatment of the truncal veins and tributary veins at separate times, but this is not considered in this review.

9.1 Review question: What is the clinical and cost effectiveness of stripping surgery compared with foam sclerotherapy in people with truncal leg varicose veins?

For full details see review protocol in appendix C.

Table 58: PICO characteristics of review question

Population	Adults with truncal leg varicose veins
Intervention/s	Stripping surgery [±phlebectomy]
Comparison/s	Foam sclerotherapy: ± crossectomy (ligation)
Outcomes	• Patient-reported outcome:- ○ Health-related quality of life ○ Patient-assessed symptoms • Physician-reported outcomes • Presence of reflux • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work/normal activities
Study design	Randomised Controlled Trials

9.1.1 Clinical evidence

We searched for RCTs comparing the effectiveness of stripping surgery in comparison to foam sclerotherapy as interventions for improving outcomes for people with truncal leg varicose veins. We excluded studies that did not specify a varicose veins population, and sub grouped by foam sclerotherapy type (with or without crossectomy) from the outset.

We included 8 clinical trials in this review. See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 59: Summary of studies included in the review

Study	Population	Intervention	Comparison
Abela et al, 2008[2]	CEAP2 and 3 varicose veins (n=90)	Stripping surgery +crossectomy	Foam sclerotherapy + crossectomy
Bountouroglou et al, 2006[13]	>97% C2-C5 (n=58)	Stripping surgery + crossectomy	Foam sclerotherapy + crossectomy
Figuerido et al, 2009[31]	C5 (n=56)	Stripping surgery + crossectomy	Foam sclerotherapy
Kalodiki et al, 2011[46]21	C2-C6 (n=82)	Stripping surgery + crossectomy	Foam sclerotherapy + crossectomy
Liu et al, 2011[51]	C2-C6 (n=59)	Stripping surgery + crossectomy	Foam sclerotherapy + crossectomy
Rasmussen et al, 2011[84]	>96% CEAP2-3 Up to 4% CEAP 4-6 (n=248)	Stripping surgery + crossectomy	Foam sclerotherapy
Shadid et al. 2012[94]	All C2-5 (n=460)	Stripping surgery + crossectomy	Foam sclerotherapy
Wright et al, 2006[106]	CEAP2-4 (n=272)	Stripping surgery + crossectomy	Foam sclerotherapy

Table 60 Clinical evidence profile (GRADE table): stripping surgery versus foam sclerotherapy

Quality assessment						Summary of findings				
						No of patients, and group results (for dichotomous variables overall meta-analysis result given; for continuous variables separate study data are given)		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Stripping surgery Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Foam sclerotherapy Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Relative Risk (95% CI)	Absolute effect or Mean Difference (95% CI)	
SF36 Physical 4 weeks (higher better)										
1 Rasmussen 2011[84]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	48.14(7.21)[125]	49.2(7.56)[125]	-	MD 1.06 lower (2.89 lower to 0.77 higher)	MODERATE
SF36 Physical 1 year (higher better)										
1 Rasmussen 2011[84]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	53.33(5.9)[125]	51.94(7.66)[125]	-	MD 1.39 higher (0.3 lower to 3.08 higher)	MODERATE
SF36 mental 4 weeks (higher better)										
1 Rasmussen 2011[84]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	55.15(7.81)[125]	56.1(7.51)[125]	-	MD 0.95 lower (2.85 lower to 0.95 higher)	MODERATE
SF36 mental 1 year (higher better)										
1 Rasmussen 2011[84]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	55.83(6.31)[125]	54.73(8.89)[125]	-	MD 1.10 higher (0.81 lower to 3.01 higher)	MODERATE

AVVQ [MEDIAN (IQR) ONLY] at 3 months (better indicated by lower values) [As there was a baseline difference in Bountourouglou study, the change scores have been given, the more negative implying more improvement; no IQRs given for this study]										
Liu2011[51] Bountouroglou2006[13]	randomised trials	very serious[a]	NA	no serious indirectness	NA	12(8-17) [30] -12.0 [28]	9(5-16)[29] -6.1 [30]	-	no p value given. Between the two studies no clear effect seen (opposing directions of effect).	NA
AVVQ [MEDIAN (no IQR given) ONLY] at 3 years (better indicated by lower values)										
Kalodiki2011[46]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	NA	8.94[43]	4.97 [39]	-	p value unclear, but numerical results suggest a benefit for foam sclerotherapy	NA
AVVQ [MEDIAN (no IQR given) ONLY] at 5 years (better indicated by lower values)										
Kalodiki2011[46]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	NA	5.45 [43]	7.35[39]	-	p=0.015, with better value for stripping	NA
EQ-5D change from baseline to 2 years (higher better)										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	0.061(0.211)[177]	0.064(0.211)[213]	-	MD 0 higher (0.04 lower to 0.04 higher)	LOW
Pain due to varicose veins (subscale from SF36; 1 year) (Better indicated by higher values)										
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	88.77(17.11)[124]	85.11(23.45)[124]	-	MD 3.66 higher (1.45 lower to 8.77 higher)	MODERATE

Pain at 2 years										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	6/177 (3.4%)	14/213 (6.6%)	RR 0.52 (0.2 to 1.31)	32 fewer per 1000 (from 53 fewer to 20 more)	VERY LOW
Heavy/tired legs at 2 years										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	5/177 (2.8%)	6/213 (2.8%)	RR 1 (0.31 to 3.23)	0 fewer per 1000 (from 19 fewer to 60 more)	VERY LOW
Cramps at 2 years										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	8/177 (4.5%)	8/213 (3.8%)	RR 1.2 (0.46 to 3.14)	8 more per 1000 (from 20 fewer to 77 more)	VERY LOW
Pain at 1 year										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	14/188 (7.4%)	20/221 (9%)	RR 0.82 (0.43 to 1.58)	16 fewer per 1000 (from 52 fewer to 51 more)	VERY LOW
Heavy/tired legs at 1 year										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	9/188 (4.8%)	5/221 (2.3%)	RR 2.12 (0.72 to 6.2)	25 more per 1000 (from 6 fewer to 110 more)	VERY LOW
Cramps at 1 year										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	9/188 (4.8%)	10/221 (4.5%)	RR 1.06 (0.44 to 2.55)	3 more per 1000 (from 26 fewer to 67 more)	VERY LOW
Pain at 3 months										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	10/176 (5.7%)	12/217 (5.5%)	RR 1.03 (0.45 to 2.32)	2 more per 1000 (from 31 fewer to 69 more)	VERY LOW
Heavy/tired legs at 3 months										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	2/176 (1.1%)	8/217 (3.7%)	RR 0.31 (0.07 to 1.43)	26 fewer per 1000 (from 35 fewer to	VERY LOW

									15 more)	
Cramps at 3 months										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	6/176 (3.4%)	9/217 (4.1%)	RR 0.82 (0.3 to 2.27)	7 fewer per 1000 (from 30 fewer to 51 more)	VERY LOW
Overall VCSS score – change from baseline at 2 years (better indicated by lower values)										
1 Shadid 2012 [94]	randomised trials	Very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	-1.75(2.135)[177]	-1.49(2.135)[213]	-	MD 0.26 lower (0.69 lower to 0.17 higher)	LOW
VCSS - pain (1 month) - (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.93(0.53)[29]	0.89(0.51)[27]	-	MD 0.04 higher (0.23 lower to 0.31 higher)	VERY LOW
VCSS - pain (2 months) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.79(0.49)[29]	0.59(0.5)[27]	-	MD 0.2 higher (0.06 lower to 0.46 higher)	VERY LOW
VCSS - pain (6 months) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.72(0.53)[29]	0.56(0.51)[27]	-	MD 0.16 higher (0.11 lower to 0.43 higher)	VERY LOW
VCSS - oedema (1 month) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	0.69(0.6)[29]	0.7(0.54)[27]	-	MD 0.01 lower (0.31 lower to 0.29 higher)	VERY LOW
VCSS - oedema (2 months) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.59(0.63)[29]	0.56(0.64)[27]	-	MD 0.03 higher (0.3 lower to 0.36 higher)	VERY LOW

VCSS - oedema (6 months) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.55(0.63)[29]	0.48(0.64)[27]	-	MD 0.07 higher (0.26 lower to 0.4 higher)	VERY LOW
VCSS inflammation (1 month) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.76(0.44)[29]	0.89(0.32)[27]	-	MD 0.13 lower (0.33 lower to 0.07 higher)	VERY LOW
VCSS - inflammation (2 months) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.72(0.45)[29]	0.89(0.32)[27]	-	MD 0.17 lower (0.37 lower to 0.03 higher)	VERY LOW
VCSS - inflammation (6 months) (Better indicated by lower values)										
1 Figuerido 2009[31]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	0.72(0.45)[29]	0.89(0.32)[27]	-	MD 0.17 lower (0.37 lower to 0.03 higher)	VERY LOW
Presence of reflux within 3 months – crossectomy used with foam sclerotherapy										
2 Liu 2011[51] Bountouroglou 2006[13]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	7/51(13.7%)	7/57 (12.3%%) Median control risk: 12.3%	RR 1.14 (0.43 to 3.02)	17 more per 1000 (from 70 fewer to 248 more)	VERY LOW
Presence of reflux within 3 months – no crossectomy used with foam sclerotherapy										
3 Rasmussen 2011[84] Wright 2006[106] Shadid 2012 [94]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	47/405 (11.6%)	114/537 (21.2%) Median control risk: 25.8%	RR 0.59 (0.43 to 0.81)	106 fewer per 1000 (from 49 fewer to 147 fewer)	VERY LOW

Presence of reflux at >3–12 months - crossectomy used with foam sclerotherapy										
1 Liu 2011[51]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	3/26 (11.5%)	5/25 (20%)	RANDOM RR 0.58 (0.15 to 2.16)	84 fewer per 1000 (from 170 fewer to 232 more)	VERY LOW
Presence of reflux at >3–12 months – no crossectomy used with foam sclerotherapy										
4 Rasmussen 2011[84] Wright 2006[106] Figuerido 2009[31] Shadid 2012 [94]	randomised trials	very serious[a]	Serious[c]	no serious indirectness	Serious[b]	63/419 (15%)	155/547 (28.3%) Median control risk: 25.6%	RANDOM RR 0.46 (0.25 to 0.84)	138 fewer per 1000 (from 41 fewer to 192 fewer)	LOW
Presence of reflux at >1-5 years - crossectomy used with foam sclerotherapy										
1 Kalodiki 2011[46]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	9/26 (53.8%)	14/33 (57.6%)	RR 0.82 (0.42 to 1.58)	76 fewer per 1000 (from 246 fewer to 246 more)	VERY LOW
Presence of reflux at >1-5 years - no crossectomy used with foam sclerotherapy										
1 Shadid 2012[94]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	32/177 (18.1%)	45/213 (21.1%)	RR 0.86 (0.57 to 1.29)	30 fewer per 1000 (from 91 fewer to 61 more)	VERY LOW
Need for further treatment from > 3–12 months - crossectomy used with foam sclerotherapy										
1 Bountouroglou 2006[13]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	2/28 (7.1%)	4/30 (13.3%)	RR 0.54 (0.11 to 2.7)	61 more per 1000 (from 119 fewer to 227 more)	VERY LOW
Adverse Events: Major neurological event (i.e. stroke, TIA)										
1 Kalodiki 2011[46]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	0/43 (0%)	0/39 (0%)	not pooled	not pooled	LOW

Adverse Events: Phlebitis - crossectomy used with foam sclerotherapy										
2 Kalodiki 2011[46] Liu 2011[51]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	1/73 (1.4%)	6/68 (8.8%) Median control risk: 9%	RR 0.22 (0.04 to 1.23)	70 fewer per 1000 (from 86 fewer to 21 more)	VERY LOW
Adverse Events: Phlebitis – no crossectomy used with foam sclerotherapy										
2 Rasmussen 2011[84] Shadid 2012[94]	randomised trials	Serious[a]	Serious[c]	no serious indirectness	no serious imprecision	5/335 (1.5%)	34/374 (9.1%) Median control risk 9.6%	RR 0.17 (0.07 to 0.42)	80 fewer per 1000 (from 56 fewer to 89 fewer)	LOW
Adverse Events: PE - crossectomy used with foam sclerotherapy										
2 Kalodiki 2011[46] Liu 2011[51]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	0/73 (0%)	0/68 (0%)	not pooled	not pooled	LOW
Adverse Events: PE – no crossectomy used with foam sclerotherapy										
3 Rasmussen 2011[84] Wright 2006[106] Shadid 2012 [94]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	0/429 (0%)	2/552 (0.3%) Median control risk: 0.4%	RR 0.37 (0.04 to 3.53)	3 fewer per 1000 (from 4 fewer to 10 more)	VERY LOW
Adverse Events: DVT - crossectomy used with foam sclerotherapy										
2 Kalodiki 2011[46] Liu 2011[51]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	0/73(0%)	0/68 (0%)	not pooled	not pooled	LOW
Adverse Events: DVT– no crossectomy used with foam sclerotherapy										
3 Rasmussen 2011[84] Wright 2006[106] Shadid 2012 [94]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	1/429 (0.2%)	11/522 (2%) Median control risk: 0.7%	RR 0.25 (0.05 to 1.21)	5 fewer per 1000 (from 7 fewer to 1 more)	VERY LOW
Adverse Events: nerve injury/damage - crossectomy used with foam sclerotherapy										
2 Kalodiki 2011[46] Liu 2011[51]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	4/73 (5.5%)	0/68 (0%)	Peto OR 7.14 (0.99 to 51.52)	50 more per 1000 (from 10 less to 120 more)	VERY LOW

Adverse Events: nerve injury/damage – no crossectomy used with foam sclerotherapy										
3 Figuerido 2009[31] Rasmussen 2011[84] Shadid 2012[94]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	17/364 (4.7%)	2/401 (0.5%) Median control risk: 0%	RR 6.3 (1.87 to 21.2)	26 more per 1000 (from 4 more to 101 more)	LOW
Adverse Events: skin discolouration - crossectomy used with foam sclerotherapy										
2 Kalodiki 2011[46] Liu 2011[51]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	3/73 (4.1%)	3/68 (4.4%) Median control risk: 4.7%	RR 0.94 (0.19 to 4.53)	3 fewer per 1000 (from 38 fewer to 166 more)	VERY LOW
Adverse Events: skin discolouration – no crossectomy used with foam sclerotherapy										
3 Rasmussen 2011[84] Wright 2006[106] Shadid 2012 [94]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	47/429 (11%)	118/552 (21.4%) Median control risk: 5.6%	RR 0.69 (0.53 to 0.89)	17 fewer per 1000 (from 6 fewer to 26 fewer)	VERY LOW
Adverse Events: post procedure pain - crossectomy used with foam sclerotherapy										
2 Liu 2011[51] Abela 2008[2]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	72/90(80%)	15/59 (25.4%) Median control risk: 25.5%	RR 3.18 (2.01 to 5.03)	556 more per 1000 (from 258 more to 1000 more)	LOW
Adverse Events: post procedure pain – no crossectomy used with foam sclerotherapy										
1 Wright 2006[106]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	39/94 (41.5%)	73/178 (41%)	RR 1.01 (0.75 to 1.36)	4 more per 1000 (from 103 fewer to 148 more)	VERY LOW
Adverse Events: Post-procedure pain VAS 1-10 (continuous) by sclerotherapy type - foam sclerotherapy (Better indicated by lower values)										
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	2.25(2.23)[135]	1.6(2.04)[144]	-	MD 0.65 higher (0.15 to 1.15 higher)	LOW

Return to normal activities (days) medians (range)										
2 Wright 2006[106] Rasmussen 2011[84]	rando mised trials	very serious[a]	NA	no serious indirectness	NA	13 (no var)[94] 4(0-30)[124]	2(no var) [178] 1(0-30)[124]	-	-	NA
Return to work (days) medians (range)										
2 Rasmussen 2011[84] Liu 2011[51]	rando mised trials	very serious[a]	NA	no serious indirectness	NA	4.3(0-42)[124] 6(4-13)[26]	2.9(0-33)[124] 3(2-6)[28]	-	-	NA

(a) Outcomes were downgraded by one level if the weighted average number of serious methodological limitations across studies was one, and downgraded by two levels if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, inadequate allowance for drop-outs in the analysis, selective outcome reporting or unadjusted baseline inequivalence. Different outcomes are covered by different combinations of studies and therefore downgrading could vary according to the specific studies included in an outcome rating.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID, i.e. in line with two possible clinical decisions, appreciable benefit to no effect. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID, i.e. ranging all the way from appreciable benefit to harm – consistent with 3 possible clinical decisions. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

(c) Outcomes were downgraded by one level if the degree of inconsistency across studies was deemed serious (I squared 50–74%). Outcomes were downgraded by two levels if the degree of inconsistency was deemed very serious (I squared 75% or more). One outcome (Presence of reflux at >3–12 months – no crossectomy used) with an I squared of >50 was sub-grouped by CEAP classification category. This sub-grouping strategy failed to remove heterogeneity. These outcomes were therefore re-analysed using a random effects model, rather than the default fixed effect model used initially for all outcomes. The point estimate and 95% CIs given in the grade table and forest plots are those derived from the new random effects analysis. Another outcome [adverse events – phlebitis (no crossectomy)] had an I squared of >50% but because both effects were showing strong effects in one direction, this inconsistency was not thought to be important, and a fixed effect meta-analysis was used.

9.1.2 Economic Evidence

9.1.2.1 Published literature

One study was included with the relevant comparison[36]. This is summarised in the economic evidence profile below (Table 61). See also the study selection flow chart in appendix E and study evidence tables in appendix H.

Five studies were excluded[5,13,36,69,78]. These are summarised in appendix K, with reasons for exclusion given.

9.1.2.2 New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis. Stripping surgery and foam sclerotherapy were among the interventional therapies included in the model. Results are summarised in the economic evidence profile below (Table 61). Full details can be found in appendix L, and a summary in section 9.6.

Table 61: Economic evidence profile: Stripping surgery vs. foam sclerotherapy

Study	Applicability	Limitations	Other comments	Comparators	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gohel et al. 2010[36] (UK)	Directly Applicable	Potentially serious Limitations[a]	The study employed a decision analytic model with a 5 year time horizon. The model is designed as a decision tree over the first 3 months and a Markov model over 4 to 60 months, with 3-month cycles. The study focuses on patients with primary varicose veins in one leg (unilateral).	Day-case surgery versus ultrasound-guided foam sclerotherapy	£813	0.115 QALYs	ICER = £7,070 per QALY gained Day-case surgery was the cost-effective option	In-patient surgery was also found to be cost effective compared to ultra-sound guided foam sclerotherapy[b]. Results are sensitive to (1) the initial costs of surgery, (2) estimates of treatment effectiveness (specifically, the odds ratio for occlusion of the great saphenous vein) and (3) the relative risk of retreating residual varicosities after sequential versus concomitant phlebectomy[c].
NCGC model	Directly Applicable	Minor Limitations[d]	A markov model with one month cycles and a 5 year time horizon was built. The study focused on patients for whom surgery, endothermal treatment, foam sclerotherapy and conservative care were all possible treatments.	Day case surgery verses ultrasound-guided foam sclerotherapy	£504	0.02 QALYs	ICER = £25,200 per QALY gained. Foam sclerotherapy was the cost-effective option[e]	Univariate and probabilistic sensitivity analyses were carried out. In none of the investigated scenarios did surgery or foam sclerotherapy appear cost effective compared to endothermal treatment. Foam sclerotherapy had a probability of being cost-effective of 23%, and surgery had a probability of being cost-effective of 3%.

(d) Modelling was undertaken over a 5 year time horizon, yet the costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months. All treatments of residual varicosities with ultrasound-guided foam sclerotherapy at 3 months are assumed to be successful.

(e) However inpatient surgery was not cost effective compared to other interventions considered in the analysis –full results are presented in the economic evidence table in appendix H

(f) These results apply to the complete analysis of 8 comparators, rather than to the pairwise comparison of day case surgery compared to foam sclerotherapy

(g) Estimated rates of top-up treatment based on GDG estimates, short time horizon of 5 years

(a) However, when considering all the comparators included in the model endothermal treatment was the cost-effective option

9.1.3 Evidence statements

9.1.3.1 Clinical

Quality of life

SF-36 Physical 4 weeks

- 1 study comprising 250 participants found that stripping led to a relative harm compared to foam sclerotherapy in terms of physical quality of life at 4 weeks, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [MODERATE QUALITY].

SF-36 Physical 1 year

- 1 study comprising 250 participants found that stripping led to a relative benefit compared to foam sclerotherapy in terms of physical quality of life at one year, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [MODERATE QUALITY].

SF-36 mental 4 weeks

- 1 study comprising 250 participants found that stripping led to a relative harm compared to foam sclerotherapy in terms of mental quality of life at 4 weeks, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [MODERATE QUALITY].

SF-36 mental 1 year

- 1 study comprising 250 participants found that stripping led to a relative benefit compared to foam sclerotherapy in terms of mental quality of life at one year, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [MODERATE QUALITY].

EQ-5D – change from baseline to 2 years

- 1 study comprising 390 participants found that stripping and foam sclerotherapy did not differ in their effects on quality of life [LOW QUALITY].

AVVQ at 3 months

- 2 studies using median data, comprising 107 participants, found conflicting results concerning the effects of stripping and foam sclerotherapy on AVVQ at 3 months. Overall, no clear effect was observed [Quality rating not possible as no imprecision measure].

AVVQ at 3 years

- 1 study using median data, comprising 82 participants, found lower (better) AVVQ scores at 3 years for foam sclerotherapy compared to stripping. However no statistical tests were carried out to evaluate the precision of this point estimate [Quality rating not possible as no imprecision measure].

AVVQ at 5 years

- 1 study using median data, comprising 82 participants, found lower (better) AVVQ scores at 5 years for stripping compared to foam sclerotherapy. Non parametric statistical testing showed a high probability that the direction of this effect would be the same at the population level [Quality rating not possible as no imprecision measure].

Patient-assessed symptoms

Pain due to varicose veins (continuous variable - subscale from SF-36) (no crossectomy used with sclerotherapy)

- 1 study comprising 248 participants found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the increase in pain due to varicose veins, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [MODERATE QUALITY].

Pain

- 3 month follow-up: 1 study comprising 393 participants found that stripping and foam sclerotherapy did not differ in their effects on the level of leg pain due to varicose veins [VERY LOW QUALITY].
- 1 year follow-up: 1 study comprising 409 participants found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the risk of pain due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 2 year follow-up: 1 study comprising 390 participants found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the risk of pain due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Heavy/tired legs at 2 years

- 3 month follow-up: 1 study comprising 393 participants found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the risk of heaviness or tiredness due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 1 year follow-up: 1 study comprising 409 participants found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the risk of heavy/tired legs due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 2 year follow-up: 1 study comprising 390 participants found that stripping and foam sclerotherapy did not differ in their effects on the level of leg heaviness or tiredness due to varicose veins [VERY LOW QUALITY].

Cramps at 2 years

- 3 month follow-up: 1 study comprising 393 participants found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the risk of cramps due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 1 year follow-up: 1 study comprising 409 participants found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the risk of cramps due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 2 year follow-up: 1 study comprising 390 participants found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the risk of cramps due to varicose veins but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Physician-reported outcomes

Overall VCSS score – change from baseline to 2 years

- 1 study comprising 390 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the reduction in VCSS overall score, but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

VCSS –pain (no crossectomy used with foam sclerotherapy)

- 1 month follow-up: 1 study comprising 56 randomised legs found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the level of pain due to varicose veins at 1 month (VCSS) but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 2 months follow-up: 1 study comprising 56 randomised legs found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the level of pain due to varicose veins at 2 months (VCSS) but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- 6 months follow-up: 1 study comprising 56 randomised legs found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the level of pain due to varicose veins at 6 months (VCSS) but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

VCSS –oedema (no crossectomy used with foam sclerotherapy)

- *1 month follow-up:* 1 study comprising 56 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the level of oedema due to varicose veins at 1 month (VCSS) but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- *2 months follow-up:* 1 study comprising 56 randomised legs found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the level of oedema due to varicose veins at 2 months (VCSS) but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- *6 months follow-up:* 1 study comprising 56 randomised legs found that stripping led to a relative worsening compared to foam sclerotherapy in terms of the level of oedema due to varicose veins at 6 months (VCSS) but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

VCSS –inflammation (no crossectomy used with foam sclerotherapy)

- *1 month follow-up:* 1 study comprising 56 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the level of inflammation due to varicose veins at 1 month (VCSS) but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- *2 months follow-up:* 1 study comprising 56 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the level of inflammation due to varicose veins at 2 months (VCSS) but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].
- *6 months follow-up:* 1 study comprising 56 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in terms of the level of inflammation due to varicose veins at 6 months (VCSS) but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Presence of Reflux

Presence of reflux within 3 months (crossectomy used with foam sclerotherapy)

- 2 studies comprising 108 randomised legs found that stripping led to a relative worsening compared to foam sclerotherapy in the rate of reflux at 0-3 months, but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Presence of reflux within 3 months (no crossectomy used with foam sclerotherapy)

- 3 studies comprising 942 randomised legs found that stripping led to an improvement compared to foam sclerotherapy in the rate of reflux at 0-3 months. This was not a large enough effect to show a clearly appreciable clinical benefit of using stripping [VERY LOW QUALITY].

Presence of reflux at > 3–12 months (crossectomy used with foam sclerotherapy)

- 1 study comprising 51 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of reflux at >3 months to 1 year, but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Presence of reflux at > 3–12 months (no crossectomy used with foam sclerotherapy)

- 4 studies comprising 966 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of reflux at >3 months to 1 year. This was not a large enough effect to show a clearly appreciable clinical benefit of using stripping [LOW QUALITY].

Presence of reflux at >1-5 years (crossectomy used with foam sclerotherapy)

- 1 study comprising 59 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of reflux at 5 years but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Presence of reflux at >1-5 years (no crossectomy used with foam sclerotherapy)

- 1 study comprising 390 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of reflux at 2 years but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Need for additional/further treatment

Need for further treatment from > 3–12 months (crossectomy used with foam sclerotherapy)

- 1 study comprising 58 randomised legs found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of the need for further treatment from >3 to 12 months but the uncertainty of this effect is far too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Adverse events

Major neurological event (i.e. stroke) (crossectomy used with foam sclerotherapy)

- 1 study comprising 82 participants found that no patients in either group had a serious neurological event [LOW QUALITY].

Phlebitis (crossectomy used with foam sclerotherapy)

- 2 studies comprising 141 participants found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of phlebitis but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Phlebitis (no crossectomy used with foam sclerotherapy)

- 2 studies comprising 709 participants found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of phlebitis. This was a large enough effect to show a clearly appreciable clinical harm of using foam sclerotherapy [LOW QUALITY].

Pulmonary embolism (crossectomy used with foam sclerotherapy)

- 2 studies comprising 141 participants found no episodes of pulmonary embolism in either group, and so an effect could not be estimated [LOW QUALITY].

Pulmonary embolism (no crossectomy used with foam sclerotherapy)

- 3 studies comprising 981 participants found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of PE, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

DVT (crossectomy used with foam sclerotherapy)

- 2 studies comprising 141 participants found no episodes of DVT in either group, and so an effect could not be estimated [LOW QUALITY].

DVT (no crossectomy used with foam sclerotherapy)

- 3 studies comprising 951 participants found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of DVT, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Nerve injury/repair (crossectomy used with foam sclerotherapy)

- 2 studies comprising 141 participants found that stripping led to a relative worsening compared to foam sclerotherapy in the rate of nerve injury or damage, but the uncertainty of this effect is too large from which to draw clear conclusions about benefit and harm [VERY LOW QUALITY].

Nerve injury/repair (no crossectomy used with foam sclerotherapy)

- 3 studies comprising 765 participants found that stripping led to a relative worsening compared to foam sclerotherapy in the rate of nerve injury or damage. This was a large enough effect to show a clearly appreciable clinical harm of using stripping [LOW QUALITY].

Skin discolouration (crossectomy used with foam sclerotherapy)

- 2 studies comprising 141 participants found that stripping and foam sclerotherapy did not differ in the rate of skin discolouration [VERY LOW QUALITY].

Skin discolouration (no crossectomy used with foam sclerotherapy)

- 3 studies comprising 981 participants found that stripping led to a relative improvement compared to foam sclerotherapy in the rate of skin discolouration. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using stripping [VERY LOW QUALITY].

Post procedure pain (crossectomy used with foam sclerotherapy)

- 2 studies comprising 149 participants found that stripping led to a relative worsening compared to foam sclerotherapy in the rate of post procedure pain. This was a large enough effect to show a clearly appreciable clinical harm of using stripping [LOW QUALITY].

Post procedure pain (no crossectomy used with foam sclerotherapy)

- 1 study comprising 272 participants found that stripping and foam sclerotherapy did not differ in the rate of post procedure pain [VERY LOW QUALITY].

Post procedure pain [VAS] (no crossectomy used with foam sclerotherapy)

- 1 study comprising 279 participants found that stripping led to a relative increase compared to foam sclerotherapy in the level of post procedure pain. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using foam sclerotherapy [LOW QUALITY].

Return to work

Return to normal activities

- 2 studies using median data, comprising 520 participants, found a faster return to normal activities for foam sclerotherapy compared to stripping. However no statistical tests were carried out to evaluate the precision of this point estimate [Quality rating not possible as no imprecision measure].

Return to work

- 2 studies using median data, comprising 302 participants, found a faster return to work for foam sclerotherapy compared to stripping. However no statistical tests were carried out to evaluate the precision of this point estimate [Quality rating not possible as no imprecision measure].

9.1.3.2 Economic

One study found day case surgery and in-patient surgery to be cost-effective compared to foam sclerotherapy, however only day case surgery was cost-effective when all comparators were considered. This evidence is directly applicable with potentially serious limitations.

Our original economic analysis found foam sclerotherapy to be cost-effective compared to surgery, however neither foam sclerotherapy nor surgery were cost-effective compared to endothermal treatment. This evidence is directly applicable with minor limitations.

9.2 Review question: What is the clinical and cost effectiveness of stripping surgery compared with endothermal ablation in people with truncal leg varicose veins?

For full details see review protocol in appendix C.

Table 62: PICO characteristics of review question

Population	Adults with truncal leg varicose veins.
Intervention/s	Stripping surgery [± phlebectomy] [NOTE: Stripping surgery comes hand-in-hand with ligation, i.e. it is normal practice for ligation to occur before stripping]
Comparison/s	Endothermal ablation, including: • radiofrequency ablation • endovenous laser ablation • steam ablation [± foam sclerotherapy/phlebectomy (for tributaries)]
Outcomes	• Patient-reported outcome: ○ Health-related quality of life ○ Patient-assessed symptoms • Physician-reported outcomes • Presence of reflux: • Need for additional/further treatment

	• Adverse events from intervention • Prevention of complications from varicose veins • Return to work/normal activity
Study design	Randomised Controlled Trials

9.2.1 Clinical evidence

Sixteen relevant publications were identified comparing stripping surgery and endothermal ablation in patients with primary varicose veins. After examination of the papers it was found that these 16 publications referred to 12 different randomised controlled trials. Table 63 summarises the publications relating to each trial, the populations, details of the different endothermal ablation techniques used, and follow-up times. One additional clinical trial was selected which compared endothermal ablation (radiofrequency) to stripping surgery in a group restricted to patients with recurrent varicose veins[40].

See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

The review is divided into sections:

1. Section 9.2.1.1: Endothermal vs. stripping surgery for of patients with primary varicose veins, and
2. Section 9.2.1.2: Endothermal vs. stripping surgery for patients with recurrent varicosities

Table 63: Summary of studies included in the review

Study	Trial Group	N patients (n participants' legs)	Majority CEAP grades	Age range or mean	Type of endothermal ablation	longest follow-up point (months)
Carradice 2011[18]	Hull Endovenous Laser project 1; HELP -1	280(280)	2	49	Laser	12
Carradice 2011A[19]		280(280)	2	49	Laser	12
Darwood 2008[23]	Individual trial	118(136)	2	30-59	Laser	12
El Kaffas 2011[39]	Individual trial	180 (unclear but probably 180)	2	Approx. 34	Radiofrequency	24
Flessenkamper 2012[33]	Individual trial	301	2	48	Laser	2
Hinchcliffe 2006[40]	Individual trial	16 (all bilateral 32 – intra-patient randomisation)[a]	2	44-66	Radiofrequency	12
Lurie 2003[52]	Short and long term results of the EVOLVeS trial	85 (86)	2	Approx. 48	Radiofrequency	4
Lurie 2005[53]		unclear (65)	2	Approx. 48	Radiofrequency	24
Pronk 2010[79]	Individual trial	122(130)	3	Approx. 49	Laser	12
Rasmussen 2007[82]	Short and longer term results of a single trial	121(137)	2	22-79	Laser	6
Rasmussen 2010[83]		121(137)	2	22-79	Laser	24
Rasmussen 2011[84]	Short and longer term results of a single trial	375 (435)	2-3	18-75	Laser and Radiofrequency [c]	12
Rass 2011[85]	Individual trial	346[b]	3	Approx. 48	Laser	24
Rautio 2002[87]	Short and longer term results of a single trial	28 (28)	not stated	Approx. 35	Radiofrequency	1.8
Perala 2005[77]		28 (28)	not stated	Approx. 35	Radiofrequency	36
Stotter 2006[98]	Individual trial	60 (60)	not stated	Approx. 47	Radiofrequency	12
Subramonia 2010[100]	Individual trial	93 (93)	2	46	Radiofrequency	1.25

(a) This study was restricted to patients with recurrent varicose vein. Bilateral means both legs were affected

(b) There were some bilateral cases, but actual numbers not reported in the study. If bilateral, randomised to the same treatment. Bilateral means both legs were affected

(c) Rasmussen 2011 reports the results for laser and radiofrequency separately and are not combined. Therefore the results are presented separately in this review

9.2.1.1 Stripping surgery vs. endothermal ablation for patients with primary varicose veins

Table 64: Clinical evidence profile (GRADE table): Patients with primary varicose veins: stripping surgery versus endothermal ablation

Quality assessment						Summary of findings				
						No of legs, and group results (for dichotomous variables overall meta-analysis result given; for continuous variables separate study data are given)		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Endothermal Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Stripping surgery Mean (sd) [n]* OR median (IQR) [n] OR frequency (%)	Relative Risk (95% CI)	Absolute effect / Mean Difference (95% CI)	
Global Quality of Life - follow-up 1-12 weeks (Better indicated by lower values, and negative change = improvement) [Note that Subramonia 2010 used AVVQ, whilst Rass 2012 and Lurie 2003 used CIVIQ -2 – hence the use of standardised mean differences]										
3 LURIE 2003[52] SUBRAMONIA 2010[100] RASS2011[85]	randomised trials	very serious[a]	very serious[b]	no serious indirectness	Serious[c]	-9.2 (15.088) [43] -9.12(6.41) [47] 12.8(14)[43]	3.7(15) [36] -8.24(6.41) [41] 18(16)[37]	-	Random effects SMD 0.43 lower (0.84 to 0.02 lower)	VERY LOW
CIVIQ 2 - follow-up 1 year (Better indicated by lower values)										
1 RASS2011[85]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	10.5(14)[40]	11.1(14)32	-	Random effects SMD 0.04 higher (0.51lower to 0.42higher)	VERY LOW

CIVIQ 2 - follow-up 2years (Better indicated by lower values)										
1 RASS2011[85]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	10.8(13)[41]	9.5(11)[33]	-	Random effects SMD 0.11 higher (0.35 lower to 0.56 higher)	VERY LOW
SF-36 Physical - 4 weeks (higher better) – Laser ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	47.68 (6.95)[125]	48.13(7.21)[125]	-	MD 0.45 lower (2.21 lower to 1.31 higher)	LOW
SF-36 Physical - 4 weeks (higher better) – Radiofrequency ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	49.88(7)[125]	48.13(7.21)[125]	-	MD 1.75 higher (0.01 lower to 3.51 higher)	LOW
SF-36 mental - 4 weeks (higher better) – Laser ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	55.55(8.21)[125]	55.15(7.81)[125]	-	MD 0.40 higher (1.59 lower to 2.39 higher)	LOW
SF-36 mental - 4 weeks (higher better) - Radiofrequency ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	55.57(7.38)[125]	55.15(7.81)[125]	-	MD 0.42 higher (1.46 lower to 2.30 higher)	LOW
SF-36 Physical – 1 year (higher better) – Laser ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsisten	no serious	No serious	52.62(5.98)[125]	53.33(5.9)[125]	-	MD 0.71 lower	LOW

			cy	indirectness	imprecision				(2.18 lower to 0.76 higher)	
SF-36 Physical - 1 year (higher better) - Radiofrequency ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	53.23(5.32)[125]	53.33(5.9)[125]	-	MD 0.105 lower (1.49 lower to 1.29 higher)	LOW
SF-36 mental - 1 year (higher better) – Laser ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	56.74(5.44)[125]	55.83(6.31)[125]	-	MD 0.91 higher (0.55 lower to 2.37 higher)	LOW
SF-36 mental – 1 year (higher better) - Radiofrequency ablation										
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	56.52(6.17)[125]	55.83(6.31)[125]	-	MD 0.69 higher (0.86 lower to 2.24 higher)	LOW
Patient reported symptoms - pain at one year (dichotomous)										
1 PRONK2010[79]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	1/56 (1.8%)	6/62 (9.7%)	RR 0.18 (0.02 to 1.49)	79 fewer per 1000 (from 95 fewer to 47 more)	VERY LOW
Patient reported symptoms - oedema at one year										
1 PRONK2010[79]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	6/56 (10.7%)	10/62 (16.1%)	RR 0.66 (0.26 to 1.71)	55 fewer per 1000 (from 119 fewer to 115 more)	VERY LOW

Patient reported symptoms - dissatisfaction with body image - 1-3 years										
3 PERALA2005[77] PRONK2010[79] STOTTER2006[98]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	5/90 (5.6%)	11/94 (11.7%) Median control risk: 12.9%	RR 0.5 (0.19 to 1.32)	64 fewer per 1000 (from 104 fewer to 41 more)	VERY LOW
Physician reported disease severity - change from baseline (VCSS) <50 days (Better indicated by lower values)										
1 RAUTIO2002[87]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	-5.1(1.5) [15]	-4.4(1.1) [13]	-	MD 0.7 lower (1.67 lower to 0.27 higher)	LOW
Physician reported disease severity - change from baseline (VCSS) 3 years (Better indicated by lower values)										
1 PERALA2005[77]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	-4.3(2.3) [15]	-4(1.2) [13]	-	MD 0.3 lower (1.63 lower to 1.03 higher)	VERY LOW
Physician reported disease severity - Post-test (HVSS) 1 year (Better indicated by lower values)										
1 RASS2011[85]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	2(2)[173]	2.1(3)[143]	-	MD 0.10 lower (0.67 lower to 0.47 higher)	LOW
Physician reported disease severity - Post-test (HVSS) 2 years (Better indicated by lower values)										
1 RASS2011[85]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	2.1(3)[173]	1.9(3)[143]	-	MD 0.20 higher (0.46 lower to 0.86 higher)	LOW

Physician reported CEAP of 2 or more - 1 week FU										
1 LURIE2005[53]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	8/43 (18.6%)	6/36 (16.7%)	RR 1.12 (0.43 to 2.92)	20 more per 1000 (from 95 fewer to 320 more)	VERY LOW
VDS – asymptomatic at 2 months										
1 FLESSENKAMPER2012[33]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	84/142 (59.2%)	77/159 (48.4%)	RR 1.22 (0.99 to 1.51)	106 more per 1000 (from 5 fewer to 247 more)	LOW
Physician reported CEAP of 2 or more – 1-2 year FU										
2 LURIE2005[53] PRONK2010[79]	randomised trials	very serious[a]	Serious[b]	no serious indirectness	very serious[c]	26/92 (28.3%)	30/90 (33.3%) Median control risk: 35.4%	RR 0.84 (0.55 to 1.3)	57 fewer per 1000 (from 159 fewer to 106 more)	VERY LOW
GSV Reflux - 0-12 weeks										
8 See Forest plots for details of studies	randomised trials	very serious[a]	Serious[b]	no serious indirectness	very serious[c]	17/751 (2.3%)	24/542 (4.4%) Median control risk: 4.9%	RANDOM RR 0.48 (0.14 to 1.64)	25 fewer per 1000 (from 42 fewer to 31 more)	VERY LOW
GSV Reflux - 1-3 years										
7 See Forest plots for details of studies	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	36/513 (7%)	19/342 (5.6%) Median control risk: 5.7%	RANDOM RR 1.26 (0.71 to 2.24)	15 more per 1000 (from 17 fewer to 71 more)	VERY LOW

Adverse events - Post operative pain - Pain or tenderness within 72 hours										
4 ELKAFFAS2011[39] LURIE2003[52] SUBRAMONIA2010[100] FLESSENKAMPER2012[33]	randomised trials	very serious[a]	Serious[b]	no serious indirectness	Serious[c]	48/323 (14.9%)	67/326 (20.6%) Median control risk: 19.2%	Random effects RR 0.65 (0.51 to 0.85)	67 fewer per 1000 (from 29 fewer to 94 fewer)	VERY LOW
Adverse events - Post operative pain - Post operative pain at 7 days										
1 RASS2011[85]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	118/185 (63.8%)	91/161 (56.5%)	RR 1.13 (0.95 to 1.34)	73 more per 1000 (from 28 fewer to 192 more)	VERY LOW
Adverse events - Post operative pain - persistent tenderness (follow-up not reported)										
1 CARRADICE2011A[19]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	1/137 (0.7%)	5/133 (3.8%)	RR 0.19 (0.02 to 1.64)	30 fewer per 1000 (from 27 fewer to 24 more)	VERY LOW
Adverse events - Post operative pain (continuous) - 1 day laser (Better indicated by lower values)										
1 PRONK2010[79]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	3.58(2.6) [62]	4(2.34) [68]	-	MD 0.42 lower (1.27 lower to 0.43 higher)	VERY LOW
Adverse events - Post operative pain (continuous) – 10-14 days laser (Better indicated by lower values)										
2 PRONK2010[79] RASMUSSEN2011[84]	randomised trials	very serious[a]	very serious[b]	no serious indirectness	no serious imprecision	1.66(2.04) [62] 2.58(2.41) [143]	0.77(1.46) [68] 2.25(2.23) [123]	-	MD 0.58 higher (0.17 to 1.0 higher)	VERY LOW
Adverse events - Post operative pain (continuous) - 10-14 days radiofrequency ablation (Better indicated by lower values)										
2 RASMUSSEN2011[84] RAUTIO2002[87]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	1.21(1.72) [146] 0.7(0.5) [15]	2.25(2.23) [123] 1.7(1.3) [13]	-	MD 1.03 lower (1.43 to 0.62 lower)	LOW

Adverse events - Phlebitis/thrombophlebitis - 0-12 days										
6 CARRADICE2011A[19] DARWOOD2008[23] ELKAFFAS2011[39] RASMUSSEN2007[82] RAUTIO2002[87] RASS2011[85]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	44/565 (7.8%)	12/497 (2.4%) Median control risk: 1.2%	RR 2.86 (1.55 to 5.29)	22 more per 1000 (from 7 more to 51 more)	LOW
Adverse events - Phlebitis/thrombophlebitis - 1 month to 3 years										
3 PERALA2005[77] RASMUSSEN2007[82] RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	19/365 (5.2%)	7/214 (3.3%) Median control risk: 3%	RR 1.47 (0.64 to 3.41)	14 more per 1000 (from 11 fewer to 72 more)	VERY LOW
Adverse events - sensory deficits/ neural injury - 0-6 weeks										
12 See Forest plots for details of studies	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	67/1162 (5.8%)	78/736 (8.3%) Median control risk: 6.7%	RR 0.71 (0.53 to 0.97)	19 fewer per 1000 (from 2 fewer to 31 fewer)	VERY LOW
Adverse events - sensory deficits/ neural injury - >6 months										
3 PERALA2005[77] PRONK2010[79] RASMUSSEN2007[82]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	1/130 (0.8%)	7/130 (5.4%) Median control risk: 2%	RR 0.23 (0.05 to 1.02)	15 fewer per 1000 (from 19 fewer to 0 more)	LOW
Adverse events - DVT (0-6 weeks)										
7 See Forest plots for details of studies	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	2/920 (0.2%)	4/765 (0.5%) Median control risk: 0.6%	RR 0.51 (0.13 to 2.01)	3 fewer per 1000 (from 5 fewer to 5 more)	VERY LOW
Adverse events - limb discolourisation - 0-1 month										
4 CARRADICE2011A[19] DARWOOD2008[23] LURIE2003[52] RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	15/537 (2.8%)	9/336 (2.7%) Median control risk: 2.6%	RANDOM RR 0.87 (0.18 to 4.14)	3 fewer per 1000 (from 21 fewer to 82 more)	VERY LOW

Adverse events - limb discolourisation – 3-4 months										
2 LURIE2003[52] RASS2011[85]	randomised trials	very serious[a]	very serious[b]	no serious indirectness	very serious[c]	57/228 (25%)	22/195 (11.3%) Median control risk: 10.3%	RANDOM RR 0.76 (0.04 to 16.04)	25 fewer per 1000 (from 99 fewer to 1000 more)	VERY LOW
Adverse events – PE										
2 ELKAFFAS2011[39] STOTTER2006[98]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	N/A	0/110 (0%)	0/110 (0%)	not pooled	not pooled	LOW
Return to normal activity (days) by endothermal type - radiofrequency ablation										
2 ELKAFFAS2011[39] LURIE2003[52]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	3(3)[90] 1.36(0.92)[44]	7(2.6)[90] 6.65(6.76)[36]	-	MD: 4.15 fewer (from 4.92 fewer to 3.38 fewer)	VERY LOW
Return to normal activity (days) by endothermal type –laser										
2 RASMUSSEN2007[82] PRONK2010[79]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	6.9(7)[69] 3.2(4.3)[62]	7.7(6.1)[68] 3.2(4)[68]	-	MD: 0.24 fewer (from 1.44 fewer to 0.96 more)	LOW
Return to work (days) by endothermal type - radiofrequency ablation										
2 RAUTIO2002[87] LURIE2003[52]	randomised trials	Serious[a]	very serious[b]	no serious indirectness	Serious[c]	6.5(3.3)[15] 4.7(11.86)[44]	15.6(6)[13] 12.4(11.59)[36]	-	MD: 8.63 lower (from 11.62 lower to 5.64 lower)	LOW

Return to work (days) by endothermal type –laser										
2 RASMUSSEN2007[82] PRONK2010[79]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	7(6)[69] 4.4(5.4)[62]	7.6(4.9)[68] 4.2(3.7)[68]	-	MD: 0.15 lower (from 1.36 lower to 1.06 higher)	LOW
Return to normal activities (days) – medians (range#) #IQR for Subramonia										
3 DARWOOD2008[23] SUBRAMONIA2010[100] RASMUSSEN2011[84]	randomised trials	Serious[a]	NA	no serious indirectness	NA	2(0-7)[71] 3(2-5)[47] 2(0-25)LA[125]; 1(0-30)RF[125]	7(2-26)[32] 12.5(4-21)[41] 4(0-30)[124]	-	-	NA
Return to work (days) – medians (range#) #IQR for Subramonia										
3 DARWOOD2008[23] SUBRAMONIA2010[100] RASMUSSEN2011[84]	randomised trials	Serious[a]	NA	no serious indirectness	NA	4(1-2)[71] 10(4-13)[47] 3.6(0-46)LA[125];2.9(0-33)RF[125]	17(7.25-33.25)[32] 18.5(11-28)[41] 4.3(0-42)[124]	-	-	NA

**standardised mean differences were used where pooling from different measurement scales occurred*

(a) Outcomes were downgraded by one level if the weighted average number of serious methodological limitation s across studies was one, and downgraded by two levels if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, inadequate allowance for drop-outs in the analysis, selective outcome reporting or unadjusted baseline inequality.

(b) Outcomes were downgraded by one level if the degree of inconsistency across studies was deemed serious (I squared 50 - 74%, or chi square p value of 0.05 or less). Outcomes were downgraded by two levels if the degree of inconsistency was deemed very serious (I squared 75% or more). All outcomes with an I squared of >50 were sub grouped by 1) endothermal type and 2) CEAP classification category in turn. These sub-grouping strategies failed to remove heterogeneity in all cases, except for return to work and return to normal activities. The majority of heterogeneous outcomes were therefore re-analysed using a random effects model, rather than the default fixed effect model used initially for all outcomes. The point estimate and 95% CIs given in the grade table and forest plots are those derived from the new random effects analysis. For return to work and return to normal activities, sub-grouping by endothermal ablation type succeeded in removing heterogeneity completely.

(c) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.33 for dichotomous outcomes with a negative effect (i.e. the greater the proportion with the outcome, the worse the clinical result), at 0.8 and 1.25 for dichotomous variables with a positive effect, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

9.2.1.2 Stripping surgery vs. endothermal ablation for patients with recurrent varicose veins

Table 65: Clinical evidence profile (GRADE table): Patients with recurrent varicose veins: stripping surgery versus endothermal ablation

Quality assessment						Summary of findings				
						No of legs, and group results (for dichotomous variables overall meta-analysis result given; for continuous variables separate study data are given)		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Endothermal Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Stripping surgery Mean (sd) [n]* OR median (IQR) [n] OR frequency (%)	Relative Risk (95% CI)	Absolute effect / Mean Difference (95% CI)	
GSV reflux (6 weeks follow-up)										
1 Hinchcliffe 2006 [40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	very serious[b]	3/16 (18.8%)	2/16 (12.5%)	RR 1.5 (0.29 to 7.81)	62 more per 1000 (from 89 fewer to 851 more)	VERY LOW
Adverse events – thrombophlebitis (6 weeks)										
1 Hinchcliffe 2006[40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	very serious[b]	0/16	1/16 (6.3%)	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 414 more)	VERY LOW
Adverse events – sensory deficit / neural injury (numbness) - 6 weeks										
1 Hinchcliffe 2006 [40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	very serious[b]	2/16 (12.5%)	3/16 (18.8%)	RR 0.67 (0.13 to 3.47)	62 fewer per 1000 (from 163 fewer to 463 more)	VERY LOW

Adverse events – DVT (6 weeks)										
1 Hinchcliffe 2006 [40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	N/A	0/16	0/16	N/A	N/A	LOW
Adverse events – infection (6 weeks)										
1 Hinchcliffe 2006 [40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	very serious[b]	0/16	1/16 (6.3%)	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 414 more)	VERY LOW
Adverse events – PE (6 weeks)										
1 Hinchcliffe 2006 [40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	N/A	0/16	0/16	N/A	N/A	LOW
Adverse events – oedema (6 weeks)										
1 Hinchcliffe 2006[40]	randomised trial	Serious[a]	no serious indirectness	no serious indirectness	very serious[b]	0/16	1/16 (6.3%)	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 414 more)	VERY LOW

(a) Outcomes were downgraded by one level if the weighted average number of serious methodological limitation s across studies was one, and downgraded by two levels if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, inadequate allowance for drop-outs in the analysis, selective outcome reporting or unadjusted baseline inequality.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.33 for dichotomous outcomes with a negative effect (i.e. the greater the proportion with the outcome, the worse the clinical result), at 0.8 and 1.25 for dichotomous variables with a positive effect, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

9.2.2 Economic evidence

9.2.2.1 Published literature

One study was included that included the relevant comparison.[36] This is summarised in the economic evidence profile below (Table 66). See also the study selection flow chart in appendix E and study evidence table in appendix H.

Ten studies were selectively excluded [1,28,29,56,82,84,87,97,99,104] – these are summarised in appendix K, with reasons for exclusion given.

9.2.2.2 New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis. Stripping surgery and endothermal ablation were among the interventional therapies included in the model. Results are summarised in the economic evidence profile below (Table 66). Full details can be found in appendix L, and a summary in section 9.6.

It is clear from the economic evidence profile below that the results of the two models differ. This is partly because the effectiveness data differs between the two analyses. In the Gohel analysis, effectiveness data was based on a meta-analysis in which complete occlusion, absence of reflux and absence of recurrent varicose veins were treated as equal measures of success of varicose vein surgery. Treatment specific odds ratios were applied in order to calculate probabilities of success for each treatment. Surgery was calculated to have a higher probability of success (complete occlusion without varicosity), than endothermal techniques under local anaesthetic, and therefore led to a higher QALY gain. In contrast, the effectiveness evidence for the NCGC model was based on a systematic review and network meta-analysis (a technique which includes all relevant data rather than relying on pair-wise comparisons) of clinical recurrence data. “Success” of treatment was not considered in the model, as patients could receive top-up treatments until the treatment episode was complete. The network meta-analysis of clinical recurrence data found endothermal treatment to be the most clinically effective option, and therefore endothermal treatment resulted in a higher QALY gain than surgery.

A further difference in the two analyses was that, although modelling was undertaken over a 5 year horizon in the Gohel analysis, the costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months. The NCGC model allows for clinical recurrence, and subsequent treatment, up until the end of the 5 year time horizon.

Decisions concerning the optimal strategy are based on average cost-effectiveness, however the probability of an intervention being cost-effective is often reported to help characterise uncertainty; the optimal strategy does not always have the highest probability of being cost-effective. Interestingly, in the Gohel analysis endovenous laser ablation has the highest probability of being cost-effective. This discrepancy between the intervention with the greatest average cost-effectiveness (surgery) and that with the highest probability of being cost-effective (endovenous laser ablation), has arisen partly because the differences in costs and QALYs between interventions are effectively negligible.

Table 66: Economic evidence profile: Stripping surgery versus endothermal ablation

Study	Applicability	Limitations	Other comments	Comparators	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gohel et al. 2010 [36]	Directly applicable	Potentially serious limitations[a]	The study employed a decision analytic model with a 5 year time horizon. The study focuses on patients with primary varicose veins in only one leg (unilateral).	Surgery (DC) verses RFA (LA)	£133	0.007 QALYs	ICER = £19,012 per QALY gained. Surgery (DC) is cost-effective compared to RFA (LA).	EVLA (LA), EVLA (GA), RFA (GA) and Surgery (IP) were also analysed; Surgery (DC) was the most cost-effective option.[b] Surgery (DC) had a probability of being cost-effective of 0.29. EVLA (LA) had a probability of being the cost-effective option of 0.35, and RFA (LA) had a probability of 0.24. Economic results are most sensitive to: (1) treatment costs (2) estimates of relative treatment effectiveness with regards to saphenous vein reflux and residual varicosities and (3) the correlation between the risks of incomplete vein occlusion after treatment and residual varicosities.[c]
NCGC model	Directly Applicable	Minor Limitations[d]	A markov model with one month cycles and a 5 year time horizon was built. The study focused on adults with GSV incompetence in only one leg (unilateral).	Endothermal treatment verses surgery	-£353	0.03 QALYs	Endothermal treatment dominates surgery, providing a greater QALY gain at a lower cost.[e]	Univariate and probabilistic sensitivity analyses were carried out. In all of the investigated scenarios endothermal treatment was cost- effective compared to surgery. Endothermal treatment had a probability of being cost-effective of 71%, and surgery had a probability of being cost-effective of 3%.

(a) Although the time horizon is stated to be 5 years, the costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months. All treatments of residual varicosities with ultrasound-guided foam sclerotherapy at 3 months are assumed to be successful.

(b) Surgery (DC) refers to day-case surgery, EVLA(LA) refers to endovenous laser ablation performed under local anaesthesia, RFA(LA) refers to radiofrequency ablation performed under local anaesthesia, EVLA(GA) refers to endovenous laser ablation performed under general anaesthesia, Surgery(IP) refers to inpatient surgery and RFA(GA) refers to radiofrequency ablation performed under general anaesthesia. Full results for these treatment options are presented in the economic evidence table in appendix H. RFA (LA) was chosen here as the main comparator as it was the most cost-effective of the endothermal options.

(c) These results apply to the complete analysis of 8 comparators, rather than to the comparison of day-case surgery (DC) and RFA (LA).

(d) Estimated rates of top-up treatment based on GDG estimates, short time horizon of 5 years

(e) Endothermal was also the cost-effective strategy when all comparators included in the model were considered

9.2.3 Evidence statements

9.2.3.1 Clinical

9.2.3.1.1 Primary varicose veins

Quality of life

Global quality of life – follow-up 1-12 weeks [Note that one study used AVVQ, whilst the other two used CIVIQ -2]

- 3 studies comprising 247 participants showed that endothermal ablation was associated with a relative improvement in the level of quality of life at 1-12 weeks compared to stripping. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using endothermal ablation [VERY LOW QUALITY].

CIVIQ-2

- *1 year follow-up:* 1 study comprising 72 participants showed that endothermal ablation was associated with no clinical benefit in patient reported quality of life at up to one year compared to stripping, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *2 year follow-up:* 1 study comprising 74 participants showed that endothermal ablation was associated with a relative worsening in the level of quality of life at 2 years compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

SF-36 Physical 4 weeks (Laser)

- 1 study comprising 250 participants showed that laser endothermal ablation was associated with a relative worsening in physical quality of life at 4 weeks compared to stripping, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

SF-36 Physical 4 weeks (Radiofrequency)

- 1 study comprising 250 participants showed that RF endothermal ablation was associated with a relative improvement in physical quality of life at 4 weeks compared to stripping. However, this was not a large enough effect to show a clearly appreciable clinical benefit of using endothermal ablation [LOW QUALITY].

SF-36 mental 4 weeks (Laser)

- 1 study comprising 250 participants showed that laser endothermal ablation was associated with a relative improvement in mental quality of life at 4 weeks compared to stripping, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

SF-36 mental 4 weeks (Radiofrequency)

- 1 study comprising 250 participants showed that RF endothermal ablation was associated with a relative improvement in mental quality of life at 4 weeks compared to stripping, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

SF-36 Physical 1 year (Laser)

- 1 study comprising 250 participants showed that laser endothermal ablation was associated with a relative worsening in physical quality of life at 1 year compared to stripping, but the uncertainty

of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

SF-36 Physical 1 year (Radiofrequency)

- 1 study comprising 250 participants showed that RF endothermal ablation and stripping did not differ in physical quality of life at 1 year. [LOW QUALITY].

SF-36 mental 1 year (Laser)

- 1 study comprising 250 participants showed that laser endothermal ablation was associated with a relative improvement in mental quality of life at 1 year compared to stripping, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

SF-36 mental 1 year (Radiofrequency)

- 1 study comprising 250 participants showed that RF endothermal ablation was associated with a relative improvement in mental quality of life at 1 year compared to stripping, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

Patient-assessed symptoms

Pain at one year (dichotomous)

- 1 study comprising 118 participants' legs showed that endothermal ablation was associated with a relative reduction in the rates of patients experiencing pain compared to stripping, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Oedema at one year (dichotomous)

- 1 study comprising 118 participants' legs showed that endothermal ablation was associated with a relative reduction in the rates of patients experiencing oedema compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Dissatisfaction with body image (1-3 years)

- 3 studies comprising 184 participants' legs showed that endothermal ablation was associated with a relative reduction in the rates of patients experiencing dissatisfaction with body image at 1-3 years compared to stripping, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Physician reported disease severity

HVSS and VVCSS

- *1 year follow-up:* 1 study comprising 316 participants' legs showed that endothermal ablation and stripping surgery were not different with respect to the level of physician reported disease severity, at 1 year [LOW QUALITY].
- 2 year follow-up: 1 study comprising 316 participants' legs showed that endothermal ablation and stripping surgery were not different with respect to the level of physician reported disease severity, at 2 years [LOW QUALITY].

Change from baseline (VCSS) (<50 days)

- 1 study comprising 28 participants' legs showed that endothermal ablation was associated with a relative improvement in the level of physician reported disease severity (<50 days) compared to stripping, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

Change from baseline (VCSS) (3 years)

- 1 study comprising 28 participants' legs showed that endothermal ablation was associated with a relative improvement in the level of physician reported disease severity (3 years) compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Change in CEAP of 2 or more classes (1 week)

- 1 study comprising 79 participants' legs showed that endothermal ablation was associated with a relative increase in the rate of a CEAP of 2 or more at 1 week compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Change in CEAP of 2 or more classes(1-2 years)

- 2 studies comprising 182 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of a CEAP of 2 or more at 1-2 years compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Venous Disability Scale - asymptomatic (2 months)

- 1 study comprising 301 participants' legs showed that endothermal ablation was associated with a relative increase in the rate of being asymptomatic compared to stripping [VERY LOW QUALITY]. However, this was not a large enough effect to show a clearly appreciable clinical benefit of stripping surgery [LOW QUALITY].

Reflux

GSV reflux

- *0-12 week follow-up:* 8 studies comprising 1293 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of reflux at 0-12 weeks compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *1-3 year follow-up:* 7 studies comprising 855 participants' legs showed that endothermal ablation was associated with a relative increase in the rate of reflux at 1-3 years compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Adverse Events

Pain or tenderness within 72 hours

- 4 studies comprising 649 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of post-operative pain or tenderness within 72 hours compared to stripping. However, this was not a large enough effect to show a clearly appreciable clinical benefit of stripping surgery [VERY LOW QUALITY].

Post-operative pain at 7 days

- 1 study comprising 209 participants' legs showed that endothermal ablation was associated with a relative increase in the rate of post-operative pain at 7 days compared to stripping, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Persistent post-operative tenderness (follow-up not reported)

- 1 study comprising 270 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of persistent tenderness compared to stripping, but the

uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Post-operative pain at 1 day (continuous) (laser)

- 1 study comprising 1300 participants' legs showed that laser endothermal ablation was associated with a relative decrease in the level of post-operative pain at 1 day compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Post-operative pain at 10-14 days (continuous) (laser)

- 2 studies comprising 396 participants' legs showed that laser endothermal ablation was associated with a relative increase compared to stripping in the level of post-operative pain at 10-14 days. However, this was not a large enough effect to show a clearly appreciable clinical benefit of stripping surgery [VERY LOW QUALITY].

Post-operative pain at 10-14 days (continuous) (radiofrequency)

- 2 studies comprising 396 participants' legs showed that radiofrequency endothermal ablation was associated with a relative decrease in the level of post-operative pain at 10-14 days compared to stripping. This was a large enough effect to show a clearly appreciable clinical benefit of using radiofrequency endothermal ablation[LOW QUALITY].

Phlebitis/thrombophlebitis (0-12 days)

- 6 studies comprising 1062 participants' legs showed that endothermal ablation was associated with a relative increase in the rate of phlebitis or thrombophlebitis at 0-12 days compared to stripping. This was a large enough effect to show a clearly appreciable clinical harm of using radiofrequency endothermal ablation [LOW QUALITY].

Phlebitis/thrombophlebitis (1 month – 3 years)

- 3 studies comprising 579 participants' legs showed that endothermal ablation was associated with a relative increase in the rate of phlebitis or thrombophlebitis at 1 month to 3 years compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Sensory deficits/neural injury (0-6 weeks)

- 12 studies comprising 2098 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of sensory deficits/neural injury at 0-6 weeks compared to stripping. However, this was not a large enough effect to show a clearly appreciable clinical benefit of endothermal ablation [VERY LOW QUALITY].

Sensory deficits/neural injury (>6 months)

- 3 studies comprising 260 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of sensory deficits/neural injury at >6 months compared to stripping but the uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

DVT (0-6 weeks)

- 7 studies comprising 1685 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of DVT at 0-6 weeks compared to stripping, but only an overall 6 cases were reported (4 in stripping group and 2 in endothermal). Thus the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Limb discolouration (0-1 month)

- 4 studies comprising 873 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of limb discolouration at 0-1 month compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Limb discolouration (3-4 months)

- 1 study comprising 77 participants' legs showed that endothermal ablation was associated with a relative decrease in the rate of limb discolouration at 4 months compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Pulmonary embolism

- 3 studies comprising 252 participants' legs showed that the incidence of pulmonary embolism did not differ between endothermal ablation and stripping surgery (no events recorded for either group) [LOW QUALITY].

Return to work/normal activities

Return to normal activities by endothermal type - RF

- 2 studies comprising 260 participants' legs showed that radiofrequency endothermal ablation was associated with a decrease in the number of days to return to normal activities compared to stripping. However, this was not a large enough effect to show a clearly appreciable clinical benefit of endothermal ablation [VERY LOW QUALITY].

Return to normal activities by endothermal type - laser

- 2 studies comprising 267 participants' legs showed that laser endothermal ablation was associated with a very small decrease in the number of days to return to normal activities compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

Return to work by endothermal type - RF

- 2 studies comprising 108 participants' legs showed that radiofrequency endothermal ablation was associated with a decrease in the number of days to return to work compared to stripping. However, this was not a large enough effect to show a clearly appreciable clinical benefit of endothermal ablation [LOW QUALITY].

Return to work by endothermal type - laser

- 2 studies comprising 267 participants' legs showed that laser endothermal ablation was associated with a very small decrease in the number of days to return to work compared to stripping, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [LOW QUALITY].

Return to normal activities (median data)

- 3 studies using median data, comprising 565 participants' legs, all showed a faster return to normal activities for endothermal than stripping. In all studies, statistical testing showed the results were unlikely to be due to chance. [QUALITY not assessable as imprecision unknown].

Return to work (median data)

- 3 studies using median data, comprising 565 participants' legs, all showed a faster return to work for endothermal than stripping. In all studies, statistical testing showed the results were unlikely to be due to chance. [QUALITY not assessable as imprecision unknown].

9.2.3.1.2 Recurrent varicose veins

Reflux

GSV reflux (6 weeks)

- One study comprising 32 participants' legs showed similar rates of reflux at 1 year for endothermal and stripping surgery treatments, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Adverse events

Thrombophlebitis (6 weeks)

- One study comprising 32 participants' legs showed no cases of thrombophlebitis in the endothermal group and one in the stripping group, therefore the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Sensory deficits/neural injury – numbness and neuralgia (6 weeks)

- One study comprising 32 participants' legs showed similar rates of numbness and neuralgia at 1 year for endothermal and stripping surgery treatments, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

DVT (6 weeks)

- One study comprising 32 participants' legs reported no cases of DVT in either the endothermal or the stripping surgery treated legs [LOW QUALITY].

Infections

- One study comprising 32 participants' legs showed no cases of infection in the endothermal group and one in the stripping group, therefore the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

PE (6 weeks)

- One study comprising 32 participants' legs reported no cases of DVT in either the endothermal or the stripping surgery treated legs [LOW QUALITY].

Oedema (6 weeks)

- One study comprising 32 participants' legs showed no cases of oedema in the endothermal group and one in the stripping group, therefore the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

9.2.3.2 Economic

- One existing study found day case surgery to be cost-effective on average compared to endothermal treatment, with an ICER of £19,012 per QALY gained (day case surgery compared to radiofrequency ablation). However, endothermal treatment had a slightly higher probability of being cost-effective; effectively, the differences in costs and effects between the comparators are negligible. This evidence is directly applicable and has potentially serious limitations.
- Our original economic analysis found endothermal treatment to dominate surgery; endothermal treatment was also cost-effective when considering the other comparators in the model. This evidence is directly applicable with minor limitations.

9.3 Review question: What is the clinical and cost effectiveness of foam sclerotherapy compared with endothermal ablation in people with truncal leg varicose veins?

For full details see review protocol in appendix C.

Table 67: PICO characteristics of review question

Population	Adults with truncal leg varicose veins.
Intervention/s	Foam sclerotherapy(including ultrasound-guided foam sclerotherapy (UGFS)) [± crossectomy (ligation)] [+phlebectomy for tributaries]
Comparison/s	Endothermal ablation, including: • radiofrequency ablation • (endovenous) laser ablation (EVLA, EVLT) • steam ablation [± foam sclerotherapy/phlebectomy for tributaries]
Outcomes	• Patient-reported outcome:- ○ Health-related quality of life ○ Patient-assessed symptoms • Physician-reported outcomes • Presence of reflux • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work or return to normal activities
Study design	RCTs and observational studies

9.3.1 Clinical evidence

We searched for randomised controlled trials comparing the effectiveness of foam sclerotherapy and endovenous ablation as interventions for improving outcomes for varicose veins. Two RCTs were found (Rasmussen 2011[84] and Lattimer 2012[50]). The study by Rasmussen comprised 374 patients. As some patients had bilateral problems (e.g. both legs were affected), the numbers of legs included were 436. Though unclear, it appears that both legs from one person were always given the same treatment. This study included patients of predominantly CEAP class 2-3 (legs n=283), but also some patients of CEAP class 4-6 (legs n=20). It should be noted that the laser endothermal ablation was given in two separate ways. The first 17 patients received the 980nm diode laser, whilst the later 108 received the 1470 nm diode laser. Ages ranged from 18-75 years. The study by Lattimer comprised 110 patients, with only one leg used per participant. The CEAP class was predominantly C2-4, with a tendency towards more severe grades, particularly for the foam sclerotherapy group. All received the 1470 nm laser, and ages ranged from 21-78.

Additionally one observational study was identified[37]. This study compared endothermal laser ablation to foam sclerotherapy, but did not randomly assign patients to groups. Instead, patients were told that each treatment was equally effective and asked to make their own choice of treatment. The groups were well matched for demographic variables and VCSS, though the foam sclerotherapy group tended to have a slightly higher proportion of more severely affected patients. Ages ranged from 26-78 years.

See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

9.3.1.1 Randomised controlled trials

Table 68: Clinical evidence profile (GRADE table): RCTs of foam sclerotherapy versus endothermal ablation

Quality assessment							Summary of findings				
							No of legs, and group results (for dichotomous variables overall meta-analysis result given; for continuous variables separate study data are given)		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Foam sclerotherapy Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Endothermal ablation Mean (sd) [n]* OR median (IQR) [n] OR frequency (%)	Relative Risk (95% CI)	Absolute effect / Mean Difference (95% CI)	
SF-36 Physical - 4 weeks (higher better) – laser ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	None	49.2 (7.56)[125]	47.68 (6.95)[125]	-	MD 1.52 higher (0.28 lower to 3.32 higher)	LOW
SF-36 Physical - 4 weeks (higher better) – radiofrequency ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	None	49.2 (7.56)[125]	49.88(7)[125]	-	MD 0.68 lower (2.48 lower to 1.12 higher)	LOW
SF-36 mental - 4 weeks (higher better) – laser ablation											

1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	None	56.1(7.51)[125]	55.55(8.21)[125]	-	MD 0.55 higher (1.40 lower to 2.50 higher)	LOW
SF-36 mental - 4 weeks (higher better) – radiofrequency ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	None	56.1(7.51)[125]	55.57(7.38)[125]	-	MD 0.53 higher (1.32 lower to 2.38 higher)	LOW
SF-36 Physical – 1 year (higher better) – laser ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	No serious imprecision	None	51.93(7.66)[125]	52.62(5.98)[125]	-	MD 0.69 lower (2.39 lower to 1.01 higher)	LOW
SF-36 Physical - 1 year (higher better) – radiofrequency ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	None	51.93(7.66)[125]	53.23(5.32)[125]	-	MD 1.30 lower (2.93 lower to 0.33 higher)	VERY LOW
SF-36 mental - 1 year (higher better) – laser ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious [b]	None	54.73(8.89)[125]	56.74(5.44)[125]	-	MD 2.01 lower (3.84 lower to 0.18 lower)	VERY LOW
SF-36 mental – 1 year (higher better) - radiofrequency ablation											
1 RASMUSSEN2011[84]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	54.73(8.89)[125]	56.52(6.17)[125]	-	MD 1.79 lower (3.69 lower to 0.11 higher)	VERY LOW

Pain due to varicose veins (1 year) - taken from SF-36 - laser (Better indicated by higher values)											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85.11(23.45)[144]	88.43(19.55)[144]	-	MD 3.32 lower (8.31 higher to 1.67 higher)	MODERATE
Pain due to varicose veins (1 year) - taken from SF-36 - radiofrequency ablation (Better indicated by higher values)											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85.11(23.45)[144]	89.92(16.85)[141]	-	MD 4.81 lower (0.08 to 9.54 lower)	MODERATE
Reflux above knee 3 days – laser ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/143 (2.1%)	0/143 (0%)	Peto OR: 7.49 (0.77, 72.62)	20 more per 1000 (from 10 fewer to 50 more)	VERY LOW
Reflux above knee 3 days - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/143 (2.1%)	0/146 (0%)	Peto OR: 7.65(0.79, 74.17)	20 more per 1000 (from 10 fewer to 50 more)	VERY LOW
Reflux above knee 3-4 weeks – laser ablation											
2 Rasmussen 2011[84] Lattimer 2012	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	10/194 (5.2%)	2/194 (1%) Median control rate: 1.4%	RR 4.46 (0.94 to 21.04)	48 more per 1000 (from 1 fewer to 281 more)	LOW
Reflux above knee 4 weeks - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/144 (1.4%)	0/141 (0%)	Peto OR: 7.29(0.45, 117.1)	10 more per 1000 (from 10 fewer to 40 more)	VERY LOW

Reflux above knee 3 months – laser ablation											
1 Lattimer 2012[50]	Randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Very serious[b]	none	9/45 (20%)	9/46 (19.6%)	RR 1.02 (0.45 to 2.34)	4 more per 1000 (from 108 fewer to 263 more)	VERY LOW
Reflux above knee1 year – laser ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	20/123 (16.3%)	7/121 (5.8%)	RR 2.81 (1.23 to 6.4)	105 more per 1000 (from 13 more to 312 more)	LOW
Reflux above knee 1 year - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/123 (16.3%)	6/124 (4.8%)	RR 3.36 (1.4 to 8.08)	114 more per 1000 (from 19 more to 343 more)	MODERATE
Reflux below knee 3 weeks – laser ablation											
1 Lattimer 2012[50]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	19/45 (42.2%)	21/46 (45.7%)	RR 0.92 (0.58 to 1.47)	37 fewer per 1000 (from 192 fewer to 215 more)	VERY LOW
Need for further treatment											
1 Lattimer 2012[50]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/50 (56%)	3/50 (6%)	RR 9.33 (3.03 to 28.73)	500 more per 1000 (from 122 more to 1000 more)	MODERATE
Adverse events – pain for 7 days post Treatment – medians											

1 Lattimer 2012[50]	randomised trials	Serious[a]	NA	no serious indirectness	NA	None (estimated from non-parametric p value of <0.0005)	Median (IQR): 14(6-34)	Median (IQR): 33(18-54)	NA	Difference in medians of 19 VAS points in favour of FS (p=0.005)	NA
AVVQ at 3 months (change from baseline) – median (higher worse)											
1 Lattimer 2012[50]	randomised trials	Serious[a]	NA	no serious indirectness	NA	Serious (estimated from non-parametric p value of 0.06)	Median (IQR): -9(11)	Median (IQR): -12(11)	NA	Difference of 3 points in favour of LASER	NA
VCSS at 3 months (change from baseline) – median (higher worse)											
1 Lattimer 2012[50]	randomised trials	Serious[a]	NA	no serious indirectness	NA	Very serious (estimated from non-parametric p value of 0.82)	Median (IQR): -4(3)	Median (IQR): - 5(2)	NA	Difference of 1 point in favour of LASER	NA
Adverse events - post op pain (10 days) [VAS] - laser (Better indicated by lower values)											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	1.6(2.04)[144]	2.58(2.41)[144]	-	MD 0.98 lower (1.5 to 0.46 lower)	LOW
Adverse events - post op pain (10 days) [VAS] - radiofrequency ablation (Better indicated by lower values)											

1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1.6(2.04)[144]	1.21(1.72)[141]	-	MD 0.39 higher (0.05 lower to 0.83 higher)	MODERATE
Adverse events - DVT – laser ablation											
2 Rasmussen 2011[84] Lattimer 2012[50]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/194 (0.5%)	1/194 (0.5%)	Peto OR: 1 (0.06, 15.99)	0 more per 1000 (from 9 fewer to 129 more)	VERY LOW
Adverse events - DVT - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/144 (0.7%)	0/141 (0%)	Peto OR: 7.24 (0.14, 364.79)	10 more per 1000 (from 10 fewer to 30 more)	VERY LOW
Adverse events - neural injury/damage – laser ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/144 (1.4%)	3/144 (2.1%)	RR 0.67 (0.11 to 3.93)	7 fewer per 1000 (from 19 fewer to 61 more)	VERY LOW
Adverse events - neural injury/damage - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/144 (1.4%)	6/141 (4.3%)	RR 0.33 (0.07 to 1.59)	29 fewer per 1000 (from 40 fewer to 25 more)	VERY LOW
Adverse events - PE – laser ablation											

1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/144 (0.7%)	0/144 (0%)	Peto OR: 7.39 (0.15, 372.38)	10 more per 1000 (from 10 fewer to 30 more)	VERY LOW
Adverse events - PE - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/144 (0.7%)	0/141 (0%)	Peto OR: 7.24 (0.14, 364.79)	10 more per 1000 (from 10 fewer to 30 more)	VERY LOW
Adverse events - Phlebitis – laser ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/144 (11.8%)	4/144 (2.8%)	RR 4.25 (1.47 to 12.32)	90 more per 1000 (from 13 more to 314 more)	MODERATE
Adverse events - Phlebitis – radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	17/144 (11.8%)	12/141 (8.5%)	RR 1.39 (0.69 to 2.8)	33 more per 1000 (from 26 fewer to 153 more)	VERY LOW
Adverse events - hyper-pigmentation – laser ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/144 (5.6%)	3/144 (2.1%)	RR 2.67 (0.72 to 9.85)	35 more per 1000 (from 6 fewer to 184 more)	VERY LOW
Adverse events - hyper-pigmentation - radiofrequency ablation											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	8/144 (5.6%)	8/141 (5.7%)	RR 0.98 (0.38 to 2.54)	1 fewer per 1000 (from 35 fewer to 87 more)	VERY LOW
Return to normal activities – laser [MEDIAN (range) DAYS]											

2 Rasmussen 2011[84] Lattimer 2012[50]	randomised trials	Serious[a]	NA	no serious indirectness	NA	none	1(0-30)[124] 3(1-10)[50]	2(0-25)[125] 7.5(2-15)[50]	-	-	NA
Return to normal activities – radiofrequency ablation [MEDIAN (range) DAYS]											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	NA	no serious indirectness	NA	none	1(0-30)[124]	1(0-30)[125]	-	-	NA
Return to work – laser ablation[MEDIAN (range) DAYS]											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	NA	no serious indirectness	NA	none	2.9(0-33)[124]	3.6(0-46)[125]	-	-	NA
Return to work – radiofrequency ablation [MEDIAN (range) DAYS]											
1 Rasmussen 2011[84]	randomised trials	Serious[a]	NA	no serious indirectness	NA	none	2.9(0-33)[124]	2.9 (0-14)[125]	-	-	NA

(a) Outcomes were downgraded by one level if the weighted average number of serious methodological limitations across studies was one, and downgraded by two levels if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised lack of blinding.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

9.3.1.2 Observational studies

Table 69: Clinical evidence profile (GRADE table): Observational studies of foam sclerotherapy vs. endothermal ablation

Quality assessment							*No of patients*		*Effect*		
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sclerotherapy Mean (sd) [n] OR median (IQR) [n] OR frequency (%)**	**endothermal (observational) Mean (sd) [n] OR median (IQR) [n] OR frequency (%)**	**Relative Risk (95% CI)**	**Absolute effect / Mean Difference (95% CI)**	**Quality**
Reflux at 1 year											
1 Gonzalez-Zeh, 2008 [37]	observational study	Serious [a]	no serious inconsistency	no serious indirectness	Serious [b]	none	8/53 (15.1%)	1/45 (2.2%)	RR 6.79 (0.88 to 52.27)	129 more per 1000 (from 3 fewer to 1000 more)	VERY LOW
VCSS at 1 year (Median – better indicated by lower values)											
1 Gonzalez-Zeh, 2008[37]	observational study	Serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3(3-2); n=53	2(3-2); n=45	-	No p-value or other measure of effect size provided	VERY LOW
Adverse events – pain (VAS 1-10, 10 worst) (Mean (sd) – better indicated by lower values)											
1 Gonzalez-Zeh, 2008[37]	observational study	Very serious [a]	no serious inconsistency	no serious indirectness	N/A	none	4.9 (1.5); n=45	4.0 (1.5); n=53	-	MD 0.9 lower (1.5 to 0.3 lower)	VERY LOW
Adverse events – phlebitis											
1 Gonzalez-Zeh, 2008[37]	observational study	Serious [a]	no serious inconsistency	no serious indirectness	Serious [b]	none	22/53 (41.5%)	10/45 (22.2%)	RR 1.87 (0.99 to 3.52)	193 more per 1000 (from 2 fewer to 560 more)	VERY LOW

Adverse events – paraesthesia											
1 Gonzalez-Zeh, 2008[37]	observational study	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/53 (1.9%)	2/45 (4.4%)	RR 0.42 (0.04 to 4.53)	26 fewer per 1000 (from 43 fewer to 157 more)	VERY LOW
Adverse events – DVT											
1 Gonzalez-Zeh, 2008[37]	observational study	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/53 (3.8%)	0/45 (0%)	Peto OR 6.48 (0.40 to 106.04)	40 more per 1000 (from 30 fewer to 100 more)	VERY LOW

(a) Participants could decide which therapy they wanted to receive. The study limitation was downgraded twice for the outcome VCSS, since no effect measure was reported.

(b) Imprecision was downgraded once when the confidence interval of the total effect ranged from one clinical minimal important difference to no effect and downgraded twice when the confidence interval of the overall effect ranges from benefit to harm

9.3.2 Economic evidence

9.3.2.1 Published literature

One study was included that included the relevant comparison.[36] This is summarised in the economic evidence profile below (Table 70). See also the study selection flow chart in appendix E and study evidence tables in appendix H.

One study that met the inclusion criteria was selectively excluded[84] – this is summarised in appendix K, with reasons for exclusion given.

9.3.2.2 New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis. Foam sclerotherapy and endothermal ablation are among the interventional therapies included in the model. Results are summarised in the economic evidence profile below (Table 70). Full details can be found in appendix L, and a summary in section 9.6.

Table 70: Economic evidence profile: Foam sclerotherapy vs Endothermal Ablation

Study	Applicability	Limitations	Other comments	Comparators	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gohel et al. 2010 [36] (UK)	Directly applicable	Potentially serious limitations[a]	The study employed a decision analytic model with a 5 year time horizon. The model is designed as a decision tree over the first 3 months and a Markov model over 4 to 60 months, with 3-month cycles. The study focuses on patients with primary varicose veins in only one leg (unilateral).	Radiofrequency ablation (local anaesthesia) verses foam sclerotherapy	£681	0.108 QALYs	£6,306 per QALY gained Radiofrequency ablation is cost-effective compared to ultrasound-guided foam sclerotherapy.	EVLA (LA), EVLA (GA) and RFA (GA) were also analysed[b]; all were cost-effective compared to foam sclerotherapy. [c] Results are sensitive to (1) the initial costs of surgery, (2) estimates of treatment effectiveness [specifically, the odds ratio for occlusion of the great saphenous vein] and (3) the relative risk of retreating residual varicosities after sequential versus concomitant phlebectomy.[d]
NCGC model	Directly Applicable	Minor Limitations[d]	A markov model with one month cycles and a 5 year time horizon was built. The study focused on adults with GSV incompetence in one leg (unilateral).	Endothermal treatment verses ultrasound-guided foam sclerotherapy	£151	0.05 QALYs	ICER = £3,161 per QALY gained. Endothermal treatment was the cost-effective option[e]	Univariate and probabilistic sensitivity analyses were carried out. In all of the investigated scenarios endothermal treatment was cost effective compared to foam sclerotherapy. Endothermal treatment had a probability of being cost-effective of 71%, and foam sclerotherapy had a probability of being cost-effective of 23%.

(a) Modelling was undertaken over a 5 year time horizon, yet the costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months. All treatments of residual varicosities with ultrasound-guided foam sclerotherapy at 3 months are assumed to be successful.

(b) EVLA(LA) refers to endovenous laser ablation performed under local anaesthesia, RFA(LA) refers to radiofrequency ablation performed under local anaesthesia, EVLA(GA) refers to endovenous laser ablation performed under general anaesthesia, and RFA(GA) refers to radiofrequency ablation performed under general anaesthesia. Full results for these treatment options are presented in the economic evidence table in appendix H. RFA (LA) was chosen here as the main comparator as it was the most cost-effective of the endothermal options.

(c) The full incremental analysis reported in the study suggests that the optimal strategy is day-case surgery.

(d) These results apply to the complete analysis of 8 comparators, rather than to the comparison of day-case surgery (DC) and RFA (LA).

(e) Estimated rates of top-up treatment based on GDG estimates, short time horizon of 5 years

(f) Endothermal was also the cost-effective strategy when all comparators included in the model were considered

9.3.3 Evidence statements

9.3.3.1 Clinical

Quality of life

SF-36 Physical 4 weeks - laser

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative improvement in the physical quality of life due to varicose veins at 4 weeks, compared to laser endothermal ablation, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefits and harms [LOW QUALITY].

SF-36 Physical 4 weeks - radiofrequency ablation

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the physical quality of life due to varicose veins at 4 weeks, compared to radiofrequency ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [LOW QUALITY].

SF-36 mental 4 weeks - laser

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative improvement in the mental quality of life due to varicose veins at 4 weeks, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [LOW QUALITY].

SF-36 mental 4 weeks - radiofrequency ablation

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative improvement in the mental quality of life due to varicose veins at 4 weeks, compared to radiofrequency ablation endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [LOW QUALITY].

SF-36 Physical 1 year - laser

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the physical quality of life due to varicose veins at 1 year, compared to laser endothermal ablation, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefits and harms [LOW QUALITY].

SF-36 Physical 1 year - radiofrequency ablation

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the physical quality of life due to varicose veins at 1 year, compared to radiofrequency ablation endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

SF-36 mental 1 year - laser

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the mental quality of life due to varicose veins at 1 year, compared to laser endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [VERY LOW QUALITY].

SF-36 mental 1 year - radiofrequency ablation

- 1 study comprising 250 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the mental quality of life due to varicose veins at 1 year, compared to radiofrequency ablation endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [VERY LOW QUALITY].

AVVQ change from baseline to 3 months

- 1 study using median data, comprising 91 participants' legs, showed that foam sclerotherapy was associated with a relative worsening in the quality of life due to varicose veins at 3 months, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [Quality rating not possible as no imprecision data].

Patient reported symptoms

Pain due to varicose veins at 1 year (from 'bodily pain' component of SF36) - laser

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the level of pain due to varicose veins at 1 year, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [MODERATE QUALITY].

Pain due to varicose veins at 1 year (from 'bodily pain' component of SF36) - radiofrequency ablation

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the level of pain due to varicose veins at 1 year, compared to radiofrequency endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [MODERATE QUALITY].

Physician reported outcomes

VCSS change from baseline to 3 months

- 1 study using median data, comprising 91 participants' legs, showed that foam sclerotherapy was associated with a relative worsening in the VCSS due to varicose veins at 3 months, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [Quality rating not possible as no imprecision data].

Reflux

Reflux above knee at 3 days - laser

- 1 study comprising 286 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 3 days, compared to laser endothermal ablation, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Reflux above knee at 3 days - radiofrequency ablation

- 1 study comprising 286 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 3 days, compared to radiofrequency endothermal ablation, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Reflux above knee at 3-4 weeks - laser

- 2 studies comprising 388 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 3-4 weeks, compared to laser endothermal ablation, but the uncertainty of this effect is slightly too large from which to draw clear conclusions about benefits and harms [LOW QUALITY].

Reflux above knee at 3 months - laser

- 1 study comprising 91 participants' legs showed that foam and laser endothermal ablation did not differ in their effects on above knee reflux at 3 months [VERY LOW QUALITY].

Reflux above knee at 1 month - radiofrequency ablation

- 1 study comprising 285 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 1 month, compared to radiofrequency endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Reflux above knee at 1 year - laser

- 1 study comprising 244 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 1 year, compared to laser endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [LOW QUALITY].
- 1 observational study comprising 98 participants showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 1 year, compared to laser endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [VERY LOW QUALITY].

Reflux above knee at 1 year - radiofrequency ablation

- 1 study comprising 247 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 1 year, compared to radiofrequency endothermal ablation. This was a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [MODERATE QUALITY].

Reflux below knee at 3 weeks - laser

- 1 study comprising 100 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the rate of reflux at 3 weeks, compared to radiofrequency endothermal ablation. This was a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [MODERATE QUALITY].

Reflux below knee at 3 months - laser

- 1 study comprising 91 participants' legs showed that foam sclerotherapy was associated with a relative improvement in the rate of reflux at 3 months, compared to radiofrequency endothermal ablation but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [MODERATE QUALITY].

Need for further treatment

- 1 study comprising 100 participants' legs showed that foam sclerotherapy was associated with a relative worsening in the need for further treatment, compared to radiofrequency endothermal ablation. This was a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [MODERATE QUALITY].

Adverse Events

Post-operative pain at 10 days (VAS) - laser

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative reduction in the level of pain at 10 days, compared to laser endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical benefit of foam sclerotherapy [LOW QUALITY].
- 1 observational study comprising 98 participants showed that foam sclerotherapy was associated with a relative reduction in the level of pain at 10 days, compared to laser endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical benefit of foam sclerotherapy [VERY LOW QUALITY].

Post-operative pain at 7 days [median] (VAS) - laser

- 1 study comprising 91 participants' legs showed that foam sclerotherapy was associated with a relative reduction in the level of pain at 7 days, compared to laser endothermal ablation. This was a large enough effect to show a clearly appreciable clinical benefit of foam sclerotherapy [Quality rating not possible as no imprecision data].

Post-operative pain at 10 days (VAS) - radiofrequency ablation

- 1 study comprising 285 participants' legs showed that foam sclerotherapy was associated with a relative reduction in the level of pain at 10 days, compared to radiofrequency endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [MODERATE QUALITY].

DVT - laser

- 2 studies comprising 388 participants' legs reported one case of DVT in the foam sclerotherapy and one in the laser endothermal ablation group. Thus the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms. [VERY LOW QUALITY].
- 1 observational study comprising 98 participants showed that foam sclerotherapy was associated with a relative increase (2 cases) in the rate of DVT, compared to laser endothermal ablation (0 cases), but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

DVT - radiofrequency ablation

- 1 study comprising 285 participants' legs showed one case of DVT in the foam sclerotherapy and none in the laser endothermal ablation group. Thus the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms. [VERY LOW QUALITY].

Neural injury/damage - laser

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative reduction in the rate of neural injury/damage, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].
- 1 observational study comprising 90 participants showed that foam sclerotherapy (1 case) was associated with a relative reduction in the rate of neural injury/damage, compared to laser endothermal ablation (2 cases), but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Neural injury/damage - radiofrequency ablation

- 1 study comprising 285 participants' legs showed that foam sclerotherapy was associated with a relative reduction in the rate of neural injury/damage, compared to radiofrequency endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

PE - laser

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative increase in the rate of PE, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

PE - radiofrequency ablation

- 1 study comprising 285 participants' legs showed that foam sclerotherapy was associated with a relative increase in the rate of PE, compared to radiofrequency endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Phlebitis - laser

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative increase in the rate of phlebitis, compared to laser endothermal ablation. This was a large enough effect to show a clearly appreciable clinical harm of foam sclerotherapy [MODERATE QUALITY].
- 1 observational study comprising 98 participants showed that foam sclerotherapy was associated with a relative increase in the rate of phlebitis, compared to laser endothermal ablation. However, this was not a large enough effect to show a clearly appreciable clinical harm by using foam sclerotherapy [VERY LOW QUALITY].

Phlebitis - radiofrequency ablation

- 1 study comprising 285 participants' legs showed that foam sclerotherapy was associated with a relative increase in the rate of phlebitis, compared to radiofrequency endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Hyper-pigmentation - laser

- 1 study comprising 288 participants' legs showed that foam sclerotherapy was associated with a relative increase in the rate of hyper-pigmentation, compared to laser endothermal ablation, but the uncertainty of this effect is too large from which to draw clear conclusions about benefits and harms [VERY LOW QUALITY].

Hyper-pigmentation - radiofrequency ablation

- 1 study comprising 285 participants' legs showed that foam sclerotherapy and radiofrequency endothermal ablation had a very similar effect on hyper-pigmentation [VERY LOW QUALITY].

Return to work and normal activities

Return to normal activities - laser

- 2 studies using median data, comprising 349 participants' legs, showed a faster return to work for foam sclerotherapy than laser endothermal ablation. However no statistical testing was carried out to allow estimation of the precision of this point estimate [QUALITY not assessable as imprecision unknown].

Return to normal activities - radiofrequency ablation

- 1 study using median data, comprising 249 participants' legs, showed the same times for return to work for foam sclerotherapy and radiofrequency endothermal ablation. However no statistical testing was carried out to allow estimation of the precision of this point estimate [QUALITY not assessable as imprecision unknown].

Return to work - laser

- 1 study using median data, comprising 249 participants' legs, showed a faster return to work for foam sclerotherapy than laser endothermal ablation. However no statistical testing was carried out to allow estimation of the precision of this point estimate [QUALITY not assessable as imprecision unknown].

Return to work - radiofrequency ablation

- 1 study using median data, comprising 249 participants' legs, showed the same times for return to work for foam sclerotherapy and radiofrequency endothermal ablation. However no statistical testing was carried out to allow estimation of the precision of this point estimate [QUALITY not assessable as imprecision unknown].

9.3.3.2 Economic

One existing study found endothermal treatment to be cost-effective compared to foam sclerotherapy. Endothermal treatment was however not found to be cost-effective when compared to day surgery. This evidence is directly applicable with potentially serious limitations.

Our original economic analysis found endothermal treatment to be cost-effective compared to foam sclerotherapy surgery; endothermal treatment was also cost-effective when considering the other comparators in the model. This evidence is directly applicable with minor limitations.

9.4 Review question: What is the clinical and cost effectiveness of avulsion surgery compared with foam sclerotherapy in people with tributary leg varicose veins?

For full details see review protocol in appendix C.

Population	Adults with tributary leg varicose veins.
Intervention/s	Avulsion surgery (ambulatory phlebectomy, phlebectomy)
Comparison/s	Foam sclerotherapy:(including ultrasound-guided foam sclerotherapy (UGFS))

Outcomes	• Patient-reported outcome:-
	  ○ Health-related quality of life,
	  ○ Patient-assessed symptoms
	• Physician-reported outcomes
	• Presence of reflux:
	• Need for additional/further treatment
	• Adverse events from intervention
	• Prevention of complications from varicose veins
	• Return to work/normal activities

Study design	Randomised Controlled Trial and Observational Studies

9.4.1 Clinical evidence

We searched for randomised controlled trials and observational cohort studies comparing the effectiveness of avulsion surgery and foam sclerotherapy as interventions for improving outcomes for varicose veins.

No RCTs were found that met the inclusion criteria. In addition, no cohort studies were found.

See also the study selection flow chart in appendix D and exclusion list in appendix J.

9.4.2 Economic evidence

9.4.2.1 Published literature

No relevant economic evaluations comparing avulsion surgery with foam sclerotherapy were identified.

9.4.2.2 New cost-effectiveness analysis

New analysis was not prioritised for this question.

9.4.2.3 Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness. The costs are estimated as the additional costs of tributary treatment when truncal treatment is being carried out concurrently.

Table 71: Components of avulsion phlebectomy and unit costs

Item	Unit Cost	Quantity	Sub total	Source
Surgeon, band 5 nurse and health care assistant time	£238 per hour	15 minutes	£59.50	PSSRU[20] and GDG estimate
Surgical instruments, drapes, steri strips, dressings etc.	£25-75	1	£25-75	GDG estimate
TOTAL			**£85 - 135**	

Table 72: Components of foam sclerotherapy and unit costs

Item	Unit Cost	Quantity	Sub total	Source
Surgeon and clinical nurse specialist time	£227 per hour	15 minutes	£56.75	PSSRU[20] and GDG estimate
Sclerosant	£10.25	1	£10.25	BNF62[44]
TOTAL			**£67**	

9.4.2.4 Economic considerations

We estimate, using the items and figures in Table 71 and Table 72 that the initial cost per patient for avulsions will be approximately £85-£135 and that for foam sclerotherapy is £67. Further differences in cost would arise if one treatment led to a higher probability of the need for retreatment than the other, however in the absence of clinical evidence this is not explored further.

9.4.3 Evidence statements

9.4.3.1 Clinical

No evidence was identified.

9.4.3.2 Economic

No cost-effectiveness evidence was identified.

Tributary treatment with foam sclerotherapy is likely to cost £67, whilst treatment with avulsion is likely to cost £85-£135. This cost summary does not capture the cost impact of any necessary further treatments, which may differ between these treatment modalities.

9.5 Review question: What is the clinical and cost effectiveness of truncal vein treatment accompanied by tributary treatments compared with truncal vein treatment alone in people with leg varicose veins?

For full details see review protocol in appendix C.

Table 73: PICO characteristics of review question

Population	Adults with leg varicose veins.
Intervention/s	Stripping surgery accompanied by tributary treatments (avulsion / foam sclerotherapy) OR Endothermal ablation accompanied by tributary treatments (avulsion / foam sclerotherapy) OR Foam sclerotherapy accompanied by tributary treatments (avulsion / foam sclerotherapy)
Comparison/s	The comparator in each case will be the truncal intervention, but without tributary treatment (avulsion / sclerotherapy) as an adjunct
Outcomes	• Patient-reported outcome:- ○ Health-related quality of life, using generic and disease specific validated tools ○ Patient-assessed symptoms • Physician-reported outcomes • Presence of reflux • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work / normal activities
Study design	Systematic Reviews, RCTs, observational

We searched for randomised controlled trials and cohort studies comparing the effectiveness of:

- Truncal treatments (Surgery / endothermal ablation / foam sclerotherapy) combined with a tributary treatment (sclerotherapy / avulsion)

with

- The corresponding truncal therapy applied alone.

9.5.1 Clinical evidence

Summary of included studies

1 RCT but no cohort studies were found that made the above comparison. Carradice 2009[17] compared endovenous ablation combined with stab avulsions with endovenous laser applied alone. However after 6 weeks any participants in the comparator group needing tributary treatments were given tributary treatment and so follow-up results after this point do not strictly answer the review

question. Therefore the outcomes relating to more than 6 weeks are not included in this review. Need for phlebectomy at 6 weeks was included as an outcome.

See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 74: Summary of studies included in the review

Study	n	CEAP grades	Age (Int/control)	Intervention details	Comparator	Follow-up
Carradice 2009[17]	50 (50 legs)	Not stated	51/52	Endovenous laser ablation (810nm, 14W continuous) PLUS Stab avulsions over varicose tributaries BOTH groups had compression for 5 weeks	Endovenous laser ablation (810nm, 14W continuous) only	6 weeks

Table 75. Clinical evidence profile (GRADE table): truncal treatments plus tributary treatments versus truncal treatments alone for varicose veins.

Quality assessment							Summary of findings				
							Meta-analysis result for dichotomous variables; individual study results for continuous variables.		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endothermal + tributary median (IQR) [n] OR frequency (%)	endothermal alone median (IQR) [n] OR frequency (%)	Relative (95% CI)	Absolute	
Quality of Life: AVVQ at 6 weeks (MEDIAN[IQR] data only) [lower is better]											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	Not assessable	none	median [IQR]: 7.9 (4.1, 10.7) [n=24]	median [IQR]: 13.5 (10.9, 18.1) [n=24]	p<0.001	Not assessable	NA[c]
Reflux –SFJ 1 week											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/24 (0%)	0/24 (0%)	not pooled	not pooled	MODERATE
Reflux –GSV 1 week											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/24 (0%)	0/24 (0%)	not pooled	not pooled	MODERATE
Adverse events – phlebitis											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/24 (0%)	1/24 (4.2%)	RR 0.33 (0.01 to 7.8)	28 fewer per 1000 (from 41 fewer to 283 more)	VERY LOW
Adverse events – pigmentation											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/24 (8.3%)	0/24 (0%)	Peto OR 7.72 (0.47 to 127.14)	80 more per 1000 (from 50 fewer to 210 more)	VERY LOW

Adverse events –thigh neuralgia											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/24 (4.2%)	0/24 (0%)	Peto OR 7.39 (0.15 to 372.38)	40 more per 1000 (from 70 fewer to 150 more)	VERY LOW
need for ambulatory phlebectomy at 6 weeks											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/25 (4%)	16/24 (66.7%)	RR 0.06 (0.01 to 0.42)	627 fewer per 1000 (from 387 fewer to 660 fewer)	MODERATE
Return to work (days) (MEDIAN[IQR] data only) [lower is better]											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	Not assessable	none	median [IQR]: 10 (4, 21) [n=24]	median [IQR]: 3 (1, 14) [n=24]	p=0.054	Not assessable	NA[c]
Return to normal activity (days) (MEDIAN[IQR] data only) [lower is better]											
1 Carradice 2009[17]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	Not assessable	none	median [IQR]: 8 (1, 14) [n=24]	median [IQR]: 2 (1, 5) [n=24]	p=0.166	Not assessable	NA[c]

(a) Outcomes were downgraded by one level for limitations because of a lack of blinding.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for all dichotomous variables

(c) It was not possible to assess the quality of the outcome as not all elements of the quality assessment were assessable.

9.5.2 Economic evidence

9.5.2.1 Published literature

No relevant economic evaluations comparing tributary and truncal treatment with truncal treatment alone were found.

9.5.2.2 New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

9.5.2.3 Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs of the addition of tributary treatment (avulsion surgery or sclerotherapy) to truncal treatment are provided in Table 76 and Table 77 below to aid consideration of cost effectiveness. Cost of truncal treatment alone was assumed to be equal across groups, and the costs of tributary treatment are calculated based on the additional cost of tributary treatment when truncal treatment is being carried out concurrently.

Table 76: Components of avulsion and unit costs

Item	Unit Cost	Quantity	Sub total	Source
Surgeon, band 5 nurse and health care assistant time	£238 per hour	15 minutes	£59.50	PSSRU[20] and GDG estimate
Surgical instruments, drapes, steri strips, dressings etc.	£25-75	1	£25-75	GDG estimate
TOTAL			**£85 - 135**	

Table 77: Components of foam sclerotherapy and unit costs

Item	Unit Cost	Quantity	Sub total	Source
Surgeon and clinical nurse specialist time	£227 per hour	15 minutes	£56.75	PSSRU[20] and GDG estimate
Sclerosant	£10.25	1	£10.25	British National Formulary 62[44]
TOTAL			**£67**	

9.5.2.4 Economic considerations

Clinical evidence from Carradice and colleagues (2009)[17] suggests that 66.7% of patients who did not receive concurrent tributary treatment, required this tributary treatment at 6 weeks post-surgery. Only 4% of those who did receive concurrent phlebectomy required further treatment. This indicates a substantially smaller likelihood that further treatment will be needed after endovenous laser ablation of truncal veins plus tributary treatment, when compared to truncal treatment alone.

9.5.3 Evidence statements

9.5.3.1 Clinical

Quality of life at 6 weeks (AVVQ) [MEDIAN DATA ONLY]

- 1 study comprising 48 participants showed that endovenous ablation combined with phlebectomy was associated with an improved quality of life compared to endovenous ablation alone. This was an effect showing clear clinical benefits for endovenous ablation combined with phlebectomy. However, it is unknown how precise this effect is [Quality rating was not possible as no imprecision measure].

Reflux

SFJ at 1 week

- 1 study comprising 48 participants compared endovenous ablation combined with phlebectomy with endovenous ablation applied alone for reflux at the SFJ at 1 week, but no events were recorded in either group and so effect sizes were not possible to ascertain [MODERATE QUALITY].

GSV 1 week

- 1 study comprising 48 participants compared endovenous ablation combined with phlebectomy with endovenous ablation applied alone for reflux at the GSV at 1 week, but no events were recorded in either group and so effect sizes were not possible to ascertain [MODERATE QUALITY].

Adverse events

Phlebitis

- 1 study comprising 48 participants showed that endovenous ablation combined with phlebectomy was associated with a lower rate of phlebitis compared to endovenous ablation alone, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Pigmentation

- 1 study comprising 48 participants showed that endovenous ablation combined with phlebectomy was associated with a greater rate of pigmentation compared to endovenous ablation alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Thigh neuralgia

- 1 study comprising 48 participants showed that endovenous ablation combined with phlebectomy was associated with a greater rate of thigh neuralgia compared to endovenous ablation alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Need for phlebectomy at 6 weeks

- 1 study comprising 49 participants showed that endovenous ablation combined with phlebectomy was associated with a far lower rate of phlebectomy compared to endovenous ablation alone. This was an effect showing clear clinical benefits for endovenous ablation combined with phlebectomy. [MODERATE QUALITY].

Return to work (days) [MEDIAN DATA ONLY]

- 1 study comprising 48 participants showed that endovenous ablation combined with phlebectomy was associated with a more prolonged return to work compared to endovenous ablation alone. According to the p-value the uncertainty of this effect is slightly too large from which to draw clear conclusions about relative benefit and harm, but imprecision could not be directly assessed [Quality rating not possible as no imprecision measure].

Return to normal activities (days) [MEDIAN DATA ONLY]

- 1 study comprising 48 participants showed that endovenous ablation combined with phlebectomy was associated with a more prolonged return to normal activities compared to endovenous ablation alone. According to the p-value the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm, but imprecision could not be directly assessed. [Quality rating not possible as no imprecision measure].

Economic

- No studies were found that conducted an economic evaluation comparing truncal treatment plus tributary treatment with truncal treatment alone in leg varicose veins.
- While clinical evidence suggests the addition of tributary treatment reduces the likelihood of the need for tributary treatment at 6 weeks, a cost analysis showed that adding tributary treatment would have some additional costs which range from £67 to £135.

9.6 Original economic model

9.6.1 Methods

A cost-utility analysis was undertaken where costs were considered from a UK NHS and personal social services perspective and health outcomes expressed as quality adjusted life years (QALYs). Costs and QALYs were both discounted at 3.5% per annum, in accordance with the NICE reference case.[65]

9.6.1.1 Comparators

Four treatments were considered in the base case:

- Surgery (stripping and ligation) – with or without tributary treatment, carried out as a day case procedure under general anaesthetic
- Endothermal techniques (RFA & EVLA) with concurrent phlebectomy – carried out as an outpatient procedure under local anaesthetic
- Foam sclerotherapy – with or without tributary treatment, carried out as an outpatient procedure under local anaesthetic
- Conservative care (compression therapy)

9.6.1.2 Population

Adults with primary great saphenous vein (GSV) incompetence in one leg (unilateral), who are potentially suitable for treatment by any of the four treatment options.

9.6.1.3 Time horizon

The time horizon of the model was five years in the base case.

9.6.1.4 Approach to modelling

For the purpose of the model, a combination of an initial treatment and a top-up treatment was considered to be one treatment episode. All patients in the model had an initial treatment episode, leading to an increase in quality of life (QoL). The probability of having subsequent recurrence of varicose veins differed by treatment option, and for the purpose of the model was taken from a network meta-analysis which is summarised in section 9.6.1.5.2 below (full details in appendix L). Patients could undergo a second treatment episode in the model, after which they could experience recurrence again.

9.6.1.4.1 Key definitions

A **treatment episode** consists of a treatment for every patient, and a top-up treatment for the proportion of individuals who require it. There is potential for two treatment episodes in the model; an **initial treatment episode** which all patients in the model receive, and a **second treatment episode** which is given to a proportion of individuals following clinical recurrence. The second treatment episode is distinct from top-up treatment, which is considered to be part of a treatment episode.

Top-up treatment is given as part of a treatment episode (within 2 months of the initial treatment) if treatment is not deemed to be complete (i.e. if the vein undergoing treatment has not been occluded or obliterated, or if additional treatment of residual varicosities is needed). Top-up treatment was assumed to always be foam.

Clinical recurrence is defined as development of symptoms of varicose veins in a treated limb. For the purpose of the network meta-analysis, papers which report clinical recurrence as an outcome were taken at face value.

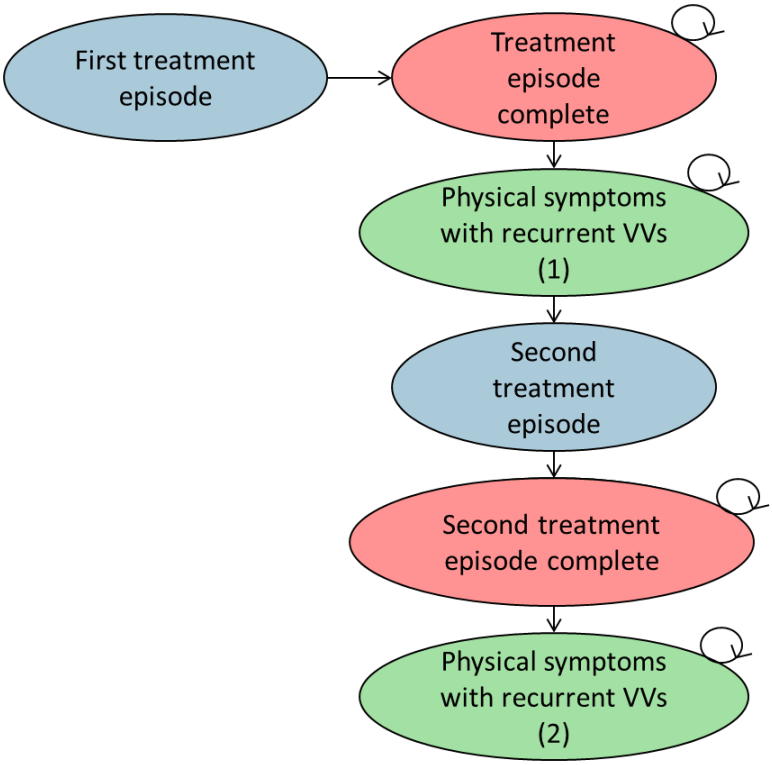
9.6.1.4.2 Model structure

A Markov model was constructed (see Figure 3). Patients enter the model through the 'First treatment episode' state. Following completion of the treatment episode, patients move to a state of 'treatment episode complete', where they do not require any further treatment. They remain in this state until they experience clinical recurrence, at which point they transition to the state 'Physical symptoms with recurrent varicose veins (1)'. Some patients go on to receive a second treatment episode, after which they can again experience clinical recurrence, but will not receive further treatment.

Conservative care was modelled separately to the other three interventions, as the outcomes of completed treatment and clinical recurrence are not clinically meaningful when considering this management technique.

The model was built with a one month cycle length as this was deemed to be the minimum clinically meaningful time interval to detect differences between interventions.

Figure 3: Model diagram



Schematic diagram of the Markov model designed to compare the cost-effectiveness of treatments for varicose veins. The Markov modelling approach involves a transition between different health states over time. The model is divided into monthly cycles. At the end of each cycle a transition to another health state is possible, unless people enter into an 'absorbing state' from which they cannot transition. In this model, the absorbing state is 'Physical symptoms with recurrent VVs (2)'.

9.6.1.4.3 Key assumptions

The model employed the key assumptions outlined in Table 78. Further rationale can be found in appendix L.

Table 78: Key assumptions

Assumption	Comment
Rates of top-up treatment are the same in the initial and second treatment episode (i.e. after retreatment)	The GDG deemed this to be a reasonable assumption
Top-up treatment is always foam	The GDG deemed this to be a reasonable simplifying assumption
Patients who have had top-up treatment have the same probability of recurrence as those who haven't had top-up	The GDG deemed this to be a reasonable simplifying assumption
Constant hazard of recurrence	This was deemed to be a reasonable simplifying assumption as the time horizon of the model is relatively short
There is a 6 month delay between the onset of clinical recurrence and the second treatment episode	This is included to reflect the time between the onset of symptoms and subsequent interventional treatment.
A patient can only receive two treatment episodes in total	This is a simplifying assumption for the model but is expected to be a fair reflection of routine clinical practice
Proportions of patients having each modality of	The method of retreatment is more likely to be

Assumption	Comment
second treatment is independent of the modality of their initial treatment	based on individual patient characteristics and the nature of the recurrence, rather than the modality of initial treatment. As the model cannot capture these factors for individual patients, the GDG deemed this to be a reasonable assumption.

9.6.1.4.4 Uncertainty

The model was built probabilistically to take account of the uncertainty surrounding each input parameter. Various sensitivity analyses were also undertaken to test the robustness of model assumptions and data sources. In these analyses, one or more inputs were changed and the analysis was rerun in order to evaluate the impact of these changes on the results of the model.

9.6.1.5 Model Inputs

9.6.1.5.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. All inputs were checked for face validity by the clinical members of the GDG. A summary of the model inputs used in the base-case analysis is provided in Table 79 and Table 80 below. More details on sources, calculations and rationale for selection can be found in appendix L.

Table 79: Summary of base-case model inputs and cohort settings

	Input	Source
Comparators	Surgery, foam sclerotherapy, endothermal with phlebectomies, conservative care	GDG consensus
Population	Adults with primary unilateral[a] GSV incompetence	GDG consensus
Initial cohort settings	Age: 50 Female: 65%	Weighted average across relevant RCTs[b]
Perspective	NHS and PSS	NICE reference case[65]
Time horizon	5 years	GDG consensus
Discount rate	Costs: 3.5% QALYs: 3.5%	NICE reference case[65]

GSV = great saphenous vein
(a) Unilateral means only one leg is affected
(b) the RCTs included in the network meta-analysis for clinical recurrence

Table 80: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Utility weights				
Primary varicose veins	0.764	Beta	$\alpha = 37600, \beta = 12800$	PROMs[42]
Change in utility (from baseline) post treatment	+0.091	Lognormal	$\mu = -2.397, \sigma = 0.0007$	PROMs[42]
Change in utility (from baseline) due to recurrent varicose veins	-0.093	Lognormal	$\mu = -2.206, \sigma = 0.0128$	Beresford 2003[6]

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Conservative care (relative to surgery at 1 year)	-0.101	Normal	μ = 0.0004, σ = 0.0198	Michaels 2006[59]
Transition probabilities				
Probability of requiring top-up treatment (within 2 months post treatment)				
Surgery	5%	Deterministic SA only		GDG estimate
Endothermal	5%	Deterministic SA only		GDG estimate
Foam Sclerotherapy	20%	Deterministic SA only		GDG estimate
Conservative care	NA			
Probability of recurrence (per month)				
Surgery	0.008331	Point estimate and uncertainty from NMA		
Endothermal	0.005833	Point estimate and uncertainty from NMA		
Foam Sclerotherapy	0.009141	Point estimate and uncertainty from NMA		
Conservative care	NA			
Cost (£)				
Surgery	£908	Gamma	See appendix L	See appendix L
Endothermal	£624	Gamma		
Foam Sclerotherapy	£315	Gamma		
Conservative care[1]	£234	Deterministic SA only		
Additional cost associated with retreatment	£417	Gamma	See appendix L	See appendix L

SA = Sensitivity analysis; NMA=network meta-analysis
[1]this is an annual cost (first year incurs an additional £15)

9.6.1.5.2 Baseline event rates and relative treatment effects

Top-up treatment rates

The proportions of patients requiring top-up after each treatment are based on GDG estimates (see Table 80).

Clinical recurrence (Network meta-analysis)

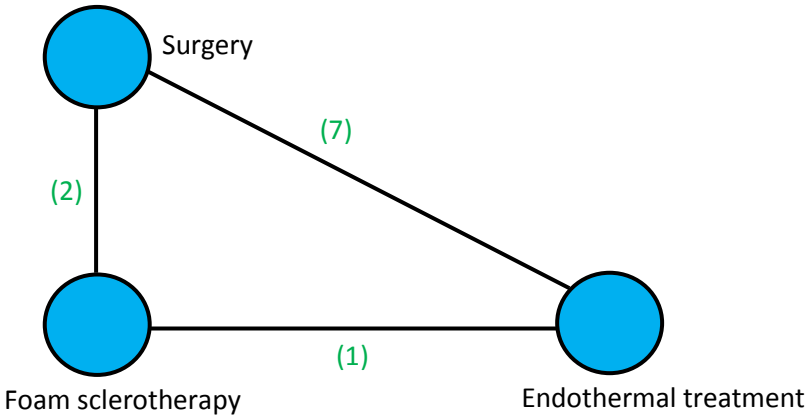
A network meta-analysis[14] was conducted to calculate treatment-specific probabilities of clinical recurrence. Key aspects of the network meta-analysis are summarised here, with full details provided in appendix L.

In order to account for the different follow-up times of the various trials, an underlying Poisson process with a constant event rate was assumed for each trial arm, and a complementary log-log (cloglog) link function used to model the event rate.

Surgery was chosen as the baseline comparator as it featured in the most trials; the baseline hazard was estimated on the clog-log scale through a meta-analysis of the surgery arms of the included trials. The resulting predictive distribution was inputted to the network meta-analysis for adjustment by the treatment specific hazard ratios to calculate the probability of clinical recurrence for each treatment. The codes for both the baseline and relative effects models were adapted from that provided on the NICE decision support unit website, and run in WinBUGS 14. The baseline and relative effects models were run for 50,000 iterations with burn in periods of 50,000.

Eight studies included in the clinical reviews of the relevant treatments included clinical recurrence as an outcome.[17,39,77,79,83-85,94]. The network of included trials is shown in Figure 4, with the number of trials included for each pair-wise comparison noted in parentheses. The included data is provided in appendix L.

Figure 4: Network of trials compared in the network meta-analysis



The final treatment-specific probability estimates and their associated confidence intervals can be seen in Table 80. It is clear from the table that endothermal treatment was associated with the lowest probability of recurrence per month. These estimates were used to parameterise treatment effects in the decision model.

9.6.1.5.3 Retreatment

Not all patients are retreated after experiencing clinical recurrence; the GDG estimated that 75% of patients would receive further interventional treatment, and it was assumed that the remaining 25% would receive conservative care. For those individuals who do undergo a second treatment episode, the mode of treatment is likely to depend on the nature of their recurrence, alongside further patient characteristics. The GDG estimated that the following proportions of patients would have each type of retreatment: 12% of retreatments would be surgery, 42% would be foam sclerotherapy and 46% would be endothermal techniques. These estimates were subject to wide ranging deterministic sensitivity analysis.

9.6.1.5.4 Adverse events

Adverse events were not included in the analysis.

9.6.1.5.5 Mortality

Patients could die at any point in the model, determined by all-cause mortality rates.[72] The mortality rates were identical for all four comparators.

9.6.1.5.6 Utilities

In cost-utility analyses, measures of health benefit are valued in terms of quality adjusted life years (QALYs). The QALY is a measure of a person's length of life weighted by a valuation of their health related quality of life (QoL) over that period. The weight used is called a utility value, which is a measurement of the preference for a particular health state, with a score usually ranging from 0 (death) to 1 (perfect health). Questionnaires such as the SF-36 and SF-12 provide generic methods of describing QoL, while the EQ-5D, HUI, and SF-6D also include preference-based valuations of each health state, allowing calculation of utility scores.

Utility inputs for the model were taken from the Patient Reported Outcome Measures (PROMs),[42] and are documented in Table 80.

The baseline value was used in the model to represent the utility of a patient with primary varicose veins, i.e. when a patient first receives treatment. The health gain post treatment was used to model the increase in utility associated with treatment. For the probabilistic analysis, the baseline value was modelled with a Beta distribution, and the health gain was modelled with a Lognormal distribution, as specified in Table 80.

Utility decrement associated with recurrent varicose veins

The quality of life associated with recurrent varicose veins was taken from Beresford and colleagues[6], and was mapped from the SF-36 data provided in the paper to EQ-5D utility scores. Recurrent varicose veins were associated with a reduction in utility of 0.093 (Table 80).

Utility for conservative care

As mentioned previously, conservative care was modelled separately to the main analysis. The difference in utility between patients undergoing surgery and conservative care was used to calculate the difference in QALYs over time between these two treatments. The difference in utility between these two treatments was taken from Michaels and colleagues[59] (see Table 81), as this was the only paper found to report such data. For the probabilistic analysis the difference between utility following conservative care and surgery was modelled using a Normal distribution to allow positive and negative differences.

Table 81: EQ-5D data for conservative care

Study	Relevant comparators	Utility values				
		Baseline	3 months	6 months	12 months	24 months
Michaels 2006[59](Group 3 only: severe varicose veins)	Surgery	0.76 (0.19)	NR	0.89 (0.13)	0.87 (0.14)	0.84 (0.21)
	Conservative care	0.77 (0.18)	NR	0.80 (0.17)	0.78 (0.18)	0.85 (0.17)

9.6.1.5.7 Resource use and costs

Costs were associated with the following health states: initial treatment episode, physical symptoms with recurrent VVs (1), second treatment episode and physical symptoms with recurrent VVs (2). The cost of the initial and second treatment episodes included the cost of a main treatment, as well as top-up treatment where applicable. The costs borne in the recurrent VVs states when no interventional treatment was being delivered were due to the on-going costs of conservative care given to people in those states.

Estimates of resource use were based on GDG estimates. Where possible, unit costs for these resources were collected from nationally available lists such as the NHS reference costs, or the PSSRU. Only NHS reference cost components were modelled probabilistically, and this was done using a Gamma distribution. A summary of the costs used in the model is presented in Table 79; the breakdown of the costs is presented in appendix L. All total costs were subject to extensive deterministic sensitivity analyses.

9.6.1.6 Bilateral treatment

The model base case only considered patients with treatment of one leg, yet consideration should also be given to treatment of patients who have both legs treated (bilateral). The model does not lend itself to bilateral analysis, therefore the GDG decided that a cost-comparison was the preferred

method to analyse the treatment of bilateral patients. Methods and results can be found in appendix L.

9.6.2 Results

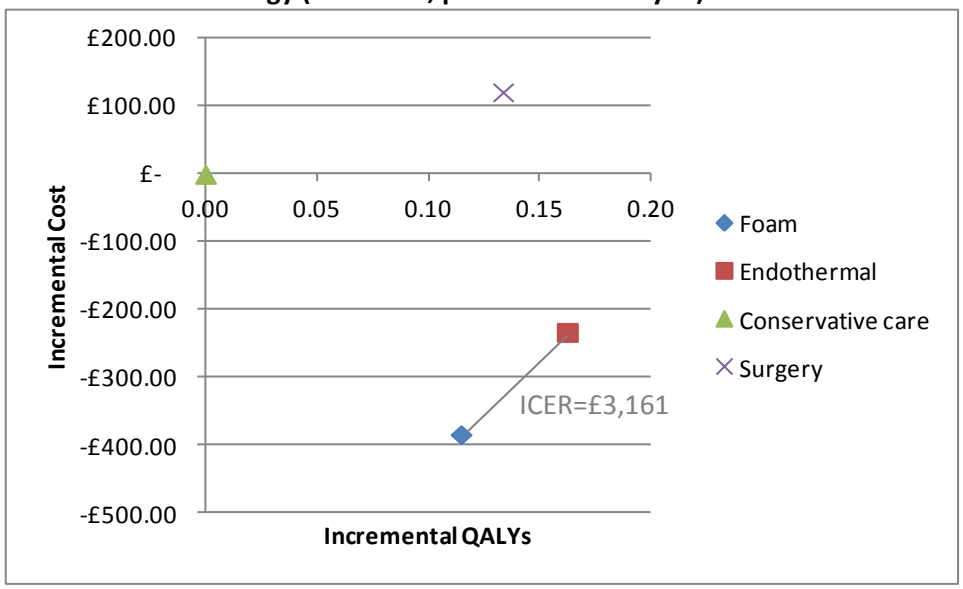
All results reported below are means from the probabilistic analysis unless otherwise specified.

Table 82 and Figure 5 show the base case results. Both conservative care and surgery were dominated, as they provided less QALYs at increased cost when compared to endothermal treatment. ICERs are not calculated for the dominated strategies.

Table 82: Mean base case results (probabilistic)

Treatment	Mean per patient		NMB at threshold of £20,000	Rank at threshold of £20,000	Probability of being CE
	QALYs	Cost			
Conservative care	3.55	£1,102	£69,965	4	4%
Surgery	3.69	£1,222	£72,554	3	3%
Foam sclerotherapy	3.67	£718	£72,681	2	23%
Endothermal	3.72	£869	£73,484	1	71%

Figure 5: Cost effectiveness plane showing incremental cost and QALYs per patient expected with each strategy (Base case, probabilistic analysis)



The strategy which provided the most QALYs, and was therefore the most clinically effective, was endothermal treatment. However, this came at an additional cost compared to foam sclerotherapy. Using the mean costs and QALYS generated over the probabilistic sensitivity analysis, the ICER of the endothermal treatment compared to foam was £3,161 which is below the NICE threshold of £20,000 per QALY gained, therefore endothermal treatment was the cost-effective strategy. Endothermal treatment had a probability of being cost-effective of 71%, followed by foam which had a lower chance of being the most cost-effective option of 23%.

9.6.2.1 Sensitivity Analyses

A wide range of sensitivity analyses were undertaken in which key assumptions and parameters were varied. None of the sensitivity analyses changed the optimum result. This shows that although

uncertainty surrounds model inputs and assumptions, variation within reasonable ranges does not change the results.

The GDG felt that area of particular uncertainty was the costs, yet sensitivity analyses revealed that the model is robust to changes in relative costs. If the costs of surgery, foam sclerotherapy and conservative care remain as specified in the base case, endothermal treatment remains cost effective even with increases in cost of up to £681

9.6.3 Discussion

A limitation of this analysis is the specific population to which it applies. The interventions considered are only true comparators when considering patients for whom all four treatments are a possibility, and in practice this may only be a small proportion of the varicose veins population. If endothermal treatment is not suitable for a patient then foam sclerotherapy is the cost-effective option, and if foam is not suitable either, surgery is the optimal strategy.

Secondly, this analysis does not attempt to answer the questions of the optimal timing of intervention, or the optimal choice of treatment at each stage of the disease. We initially hoped to address these questions, but reliable data were not available. Consequently, conclusions are applicable to the general varicose veins population, with no separate consideration of subgroups. Input data were collected from individuals at various stages of varicose veins severity, and we cannot be certain that interventional treatment is cost-effective in each subgroup. Further limitations are discussed in appendix L.

9.6.4 Economic evidence statements

- One cost-utility analysis with direct applicability and minor limitations, found day case surgery to be the cost-effective option. Day case surgery and endothermal techniques under local anaesthetic had similar probabilities of being cost-effective.
- According to the results of an original economic model based on the current clinical evidence review and GDG input, it is highly likely that endothermal treatment is the cost effective strategy for people in whom all treatments are suitable. When endothermal treatment is not deemed suitable for a patient, foam sclerotherapy is likely to be the optimal strategy. Surgery represents the optimal choice if neither endothermal treatment nor foam sclerotherapy are thought suitable. This evidence is directly applicable, with minor limitations.

9.7 Recommendations and link to evidence

9.7.1 Interventional treatment

Recommendation	**9. Offer interventional treatment to people with confirmed varicose veins and truncal reflux as follows:** • **Offer endothermal ablation.** • **If endothermal ablation is not suitable or is declined, offer ultrasound-guided foam sclerotherapy[b].** • **If ultrasound-guided foam sclerotherapy is unsuitable or is declined, offer surgery.** **If incompetent varicose tributaries are to be treated, consider treating them at the same time.**

[b] Recommendation linked to Ultrasound-guided foam sclerotherapy for varicose veins (IPG440).

	3. Does the early treatment of superficial venous reflux together with compression therapy improve wound healing and result in greater cost effectiveness compared with compression therapy alone in patients with chronic venous ulceration? **4. What is the clinical and cost effectiveness of completing concurrent phlebectomies for varicose tributaries during truncal endothermal ablation for varicose veins compared with** • **truncal endothermal ablation without concurrent phlebectomies?** • **truncal endothermal ablation with subsequent phlebectomies if needed 6-12 weeks later?** **5. What is the optimal treatment strategy (compression versus surgery versus endothermal ablation versus foam sclerotherapy) for varicose veins at the following stages of disease:** • **CEAP stages C2-C3?** • **CEAP stage C4?** • **CEAP stages C5-C6?**
Research recommendation	**6. Complete further evaluation on the systemic effect of foam sclerotherapy and endothermal ablation.**
Relative values of different outcomes	Health related quality of life and patient reports of symptoms were considered critical outcomes. Important outcomes were reflux and the need for further treatment. Reflux is a measure for treatment failure in the first few days after treatment and recurrence in the longer term. Adverse events were expected to be minor and not life threatening and were of lower priority. Time to return to normal activities and time to return to work were considered outcomes of lowest priority.
Trade-off between clinical benefits and harms	**Endothermal ablation v stripping surgery** No clinically important differences between the two interventions were noted for the critical outcomes. Post-operative pain was greater at 10-14 days for stripping surgery compared to radiofrequency ablation, but also greater at 10-14 days for laser surgery compared to stripping surgery. The GDG felt that this finding, showing both an advantage and disadvantage for stripping depending on the form of endothermal ablation used, could not influence any recommendations concerning stripping and endothermal ablation, as endothermal ablation was to be considered in the review as a single modality. The GDG also considered that the slightly lower levels of reflux and sensory deficits with endothermal ablation than stripping were not compelling enough to affect recommendations. Overall, the GDG agreed that it was not clear whether one had a benefit over the over. **Endothermal ablation v foam sclerotherapy** No clinically important differences were noted between endothermal ablation as a single modality and foam sclerotherapy for the critical outcomes. There were clear benefits for laser ablation over foam sclerotherapy in terms of mental health quality of life at 1 year. The GDG agreed there was a clinically important advantage for endothermal ablation over foam sclerotherapy in terms of reduction in reflux at 3 weeks. In contrast, they also noted a clinically important advantage for foam

	sclerotherapy compared to laser ablation in terms of post-operative pain at 10 days, although this effect was not observed in relation to radiofrequency ablation. Overall, the GDG felt that clinically endothermal ablation had a slight advantage over foam sclerotherapy. **Foam sclerotherapy v stripping surgery** No clinically important differences were noted in the critical outcomes. Where foam sclerotherapy procedures were separated into those with and without crossectomy, the GDG agreed that there was a clinically important reduction in the presence of reflux at >3 months and <12 months for stripping surgery compared to foam sclerotherapy without crossectomy. Similarly, the GDG also agreed that there was a clinically important reduction in phlebitis rates for stripping surgery compared to foam sclerotherapy without crossectomy. In contrast, there was a higher rate of nerve injury in people undergoing stripping surgery compared to foam sclerotherapy with crossectomy, which was considered clinically important. No differences were found when comparing stripping surgery to foam sclerotherapy with crossectomy. No other differences were considered clinically important. The GDG considered that the difference in reflux and the small differences in adverse events between the interventions were not compelling enough to clinically recommend one over the other. **Interventional truncal treatments with concurrent tributary treatments versus interventional truncal treatments alone** The evidence was limited to endothermal treatment and no clear differences were found for any outcomes. The GDG felt the absence of evidence on foam sclerotherapy made it impossible to make a recommendation for a preferred treatment. **Avulsions versus foam sclerotherapy for tributary treatments** There was no RCT or observational study evidence for this comparison. Overall, no recommendation was made regarding which modality was superior. **Phlebectomy** The evidence was limited for the use of phlebectomy as an adjunctive procedure to interventional truncal treatments. The GDG felt the absence of evidence made it impossible to make a recommendation referring to phlebectomy. The GDG note NICE interventional procedure guidance 37 Transilluminated powered phlebectomy for varicose veins. **Overall** After consideration of the clinical benefits and harms in each of the three pairwise truncal treatment comparisons, endothermal ablation was the only treatment judged to have any clinical advantage over the others. This is supported by the findings of the economic model and the GDG felt it was appropriate to make a strong recommendation for endothermal ablation as the preferred treatment choice. Given the lack of clear evidence that concurrent tributary treatments were beneficial, it was felt that this should be decided on an individual patient basis level. Either avulsions or foam sclerotherapy could be used for tributary treatment given the absence of efficacy evidence.
Economic considerations	An original economic model was developed to combine best available evidence on the efficacy of the various interventional treatments and conservative care for varicose veins. The primary clinical outcome included in the model was clinical recurrence after treatment, as reported in the RCTs in the clinical review**.** Costs were calculated from an NHS and social services perspective, and

	quality of life data was taken from the PROMs dataset. Endothermal ablation was found to dominate surgery and conservative care, and to be cost-effective in 71% of model simulations. Although endothermal treatment is more expensive than foam sclerotherapy, it is also more effective. The incremental cost effectiveness ratio comparing these two treatments is £3,161 per QALY gained. The model therefore found endothermal treatment to be the cost-effective treatment strategy, with foam sclerotherapy ranked second, and surgery third. The model was robust to all sensitivity analyses surrounding key assumptions and data used to inform the model. The GDG also considered one existing study, which found day-case surgery to be cost-effective compared to foam sclerotherapy, inpatient surgery, conservative care, radiofrequency ablation (local and general anaesthetic) and endovenous laser ablation (local and general anaesthetic). Day case surgery was found to have a probability of being cost-effective of 0.29, endovenous laser ablation (local) 0.35 and radiofrequency ablation 0.24. Due to the limitations of this study, specifically that costs and health outcomes associated with recurrence of varicosities are not considered beyond the first 3 months, and that all treatments of residual varicosities with ultrasound-guided foam sclerotherapy at 3 months are assumed to be successful, the GDG based the above recommendation primarily on the original economic analysis carried out for this guideline. No economic evidence was found which compared treatment of truncal veins alone versus truncal veins and tributary treatment. A simple cost analysis showed that adding tributary treatment would have some additional costs which range from £67 to £135. However the clinical evidence suggests that the addition of tributary treatment reduces the likelihood of the need for further treatment. This might generate some future cost-savings that are not captured in the analysis.
Quality of evidence	**Endothermal ablation vs stripping surgery** 17 RCTs were identified, the majority of which included patients with CEAP scores of 2-3. This implies a limited applicability to other CEAP categories. The evidence comparing stripping surgery and endothermal ablation was of low to very low quality, with much uncertainty in the direction of effects of the interventions for the majority of the outcomes. **Endothermal ablation vs foam sclerotherapy** Two RCTs and one observational study were included. The evidence for the outcomes was low to very low quality, with much uncertainty in the direction of effects of the interventions for the majority of the outcomes. **Foam sclerotherapy vs stripping surgery** Eight RCTs (with one RCT from a health technology appraisal) were included in this review. The evidence comparing stripping surgery and foam sclerotherapy was of low to very low quality, with much uncertainty in the direction of effects of the interventions for the majority of the outcomes. **Interventional truncal treatments with concurrent tributary treatments vs interventional truncal treatments alone** 1 RCT was included. Quality of evidence was moderate to very low quality. **Avulsions vs foam sclerotherapy for tributary treatments** No evidence was found.

	Overall Overall, the quality of evidence was of low to very low quality. The main limitations were methodological, such as a lack of allocation concealment or intention to treat in some studies. In addition there was a high level of imprecision for most outcomes.
Other considerations	Patient choice should be included in the decision on which form of interventional treatment is chosen. The GDG noted the on-going CLASS trial that is comparing laser, surgery and foam sclerotherapy will add to the evidence base in this area. This recommendation was chosen by the GDG as a key priority for implementation. This was because it was felt it would have a high impact on reducing variation in care and outcomes, lead to more efficient use of NHS resources, set challenging but achievable expectations of health services. **Research recommendations:** • **Does the early interventional treatment of superficial venous reflux together with compression therapy improve wound healing and result in greater cost effectiveness compared to compression therapy alone in patients with chronic venous ulceration?** This was a priority research recommendation as chronic venous leg ulcers associated with varicose veins are a common major cause of morbidity. It is thus likely that modest improvements in outcomes would result in large population and health economic benefits. Further information about this research recommendation can be found in appendix N. • **What is the clinical and cost effectiveness of concurrent phlebectomies for varicose tributaries during truncal endothermal ablation for varicose veins compared with:** ○ **truncal endothermal ablation without concurrent phlebectomies** ○ **truncal endothermal ablation with subsequent phlebectomies, if needed, 6–12 weeks later.** This was also a priority research recommendation, as this is currently an area with great variation in practice but very limited and low quality inconclusive evidence from only one RCT. The GDG felt that information gained from a large scale patient-outcome based study into endothermal treatments with or without concurrent tributary treatment could be important. This is because if treating tributaries is found to be more effective than not treating them during endothermal interventions this might influence the cost effectiveness of endothermal treatments. Further information about this research recommendation can be found in appendix N • **What is the clinical and cost effectiveness of completing interventional varicose veins treatment at different stages of the disease?** Knowledge about any optimal stage of disease at which to treat varicose veins is important, as this will influence the cost effectiveness of treatment. It had been hoped that our guideline would provide information to answer this question, through analysis of different CEAP classification sub-groups if a meta-analysis showed an inconsistent effect. However the studies consisted largely of people at lower CEAP stages, and so this was not possible. An RCT designed to investigate if there were any differential benefits or harms from treating people at different stages of varicose vein disease would therefore be beneficial. • **Complete further evaluation on the systemic effect of foam sclerotherapy**

	and endothermal ablation. Although the NICE interventional procedure guidance has identified endothermal ablation and foam sclerotherapy as safe to use under normal circumstances, a research recommendation on the systemic effects of radiofrequency and laser ablation, and foam sclerotherapy was suggested. This was based on the concerns of one of the patient members, who had concerns about the use of nanoparticles in varicose veins therapies, such as radiofrequency ablation. The members concerns arose owing to the absence of evidence concerning the: • Solubility of nanoparticles in blood • Potential for entrapment in brain-supporting tissue, • Long term effects on the blood-brain-barrier • Potential for accretion and subsequent possible adverse effects, in vital organs • Potential for side effects • Absence of assessment methods for the determination of the inhalation and absorption of nanoparticles.

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Recommendation	10. Offer compression hosiery only if interventional treatment is not suitable or is declined.

9.7.2 Compression hosiery

Research recommendation	7. What is the clinical and cost effectiveness of compression hosiery versus no compression for the management of symptomatic varicose veins?
Relative values of different outcomes	Health related quality of life was considered the most important outcome for these comparisons. Patient reported relief from symptoms associated with chronic venous insufficiency was also considered an important outcome. This included pain, ankle swelling, cramps and the feeling of having tired / heavy legs. Adverse events, such as pulmonary embolism and deep vein thrombosis, major neurological events (i.e. stroke), and local neurological events (i.e. nerve injury/damage) were considered important outcomes.
Trade off between clinical benefits and harms	The evidence for this recommendations comes from two reviews: • What is the clinical and cost effectiveness of compression therapy compared with no treatment or lifestyle advice in people with leg varicose veins? • What is the clinical and cost effectiveness of compression compared with interventional therapies (foam sclerotherapy or stripping surgery or endothermal ablation) in people with tributary leg varicose veins? **Compression versus no treatment or lifestyle advice** There was no evidence for the outcome of health related quality of life. Compression stockings reduce patient ratings of ankle swelling, cramps and the feeling of tired/ heavy legs, but these reductions are small (under 10 points on a scale ranging from 0-100). There was a clinical benefit in terms of reduced complaints in the group with compression. The GDG felt that even though some of the symptoms listed above had improved with compression treatment, results for other outcomes, such as pain relief, were less conclusive. In addition, there was no improvement in overall body image satisfaction by the use of compression hosiery. Three studies described reasons for non-adherence. The GDG considered adherence to the treatment regime important. The GDG noted that from a patient perspective negative experiences, such as the difficulty in putting on stockings could result in non-adherence. Adverse events related to compression stockings were not reported in the included studies and were considered minimal by the GDG. **Compression versus interventional treatment** The only study identified through the systematic review was for compression compared with surgery. There was evidence of benefit in terms of quality of life for surgery compared with compression, although the effect was not large enough to show clearly appreciable clinical benefit. There were clear clinical benefits for surgery in terms of patient satisfaction and patient assessed symptoms. There was a paucity of evidence for adverse events (only foot drop recorded).
Economic considerations	No health economic studies were identified. Unit costs were presented to aid consideration of cost effectiveness, which included the costs of 4 pairs of stockings per year and contact with a practice nurse. Compression was estimated to have an additional cost of £243, and would only need to offer an additional 0.012 (0.005) QALYs to be cost-effective, Given these costs and the likely improvement in quality of life, the GDG felt that compression stockings

	were likely to be cost effective compared to no treatment. Compliance with compression was highlighted as a possible confounding factor. Based on 3 studies, compression did not appear to be cost effective compared to interventional treatment. ICERs comparing surgery to conservative care were between £2,895 and £4,687 per QALY gained, based on directly applicable evidence. Original economic modelling was also carried out which compared compression to interventional treatment. Endothermal treatment was found to be the most cost-effective strategy; it dominated conservative care, providing greater QALYs at a lower cost. Full results are provided in appendix L, and a summary in chapter 9.6.
Quality of evidence	**Compression vs. no treatment or lifestyle advice** The outcomes of the 3 randomised controlled trials included in the evidence were of low to very low quality. The GDG noted the scarcity and antiquated nature of the evidence, questioning its relevance to current clinical practice. Five observational studies were included in this review and these data supported the trial findings. **Compression vs. interventional treatment** The outcomes of the one randomised controlled trial were of variable quality. Lack of blinding led to the evidence for the following outcomes; quality of life at 2 years (EQ-5D), patient satisfaction, and patient assessed symptoms being downgraded to moderate quality. Lack of blinding combined with serious imprecision led to other quality of life measures being downgraded to low quality. Lack of blinding combined with very serious imprecision led to neural adverse events being downgraded to very low quality.
Other considerations	The GDG based their recommendation on the limited low quality evidence and consensus. The GDG discussed the evidence and noted that compression stockings had a cost associated with them and the evidence of clinical benefit was weak. For this reason they felt that if a person was suitable for interventional treatment they should not be offered stockings as an alternative. In the situation where a patient was not suitable for interventional treatment or where it was the patient's choice not to undergo interventional treatment compression hosiery should be offered. The GDG discussed whether it would be possible to make recommendations about the type of compression hosiery (length and compression profile) to be offered but the evidence was not clear. Although the RCT papers had each studied different types of stocking, there had been no prior plans for sub-grouping by stocking type if heterogeneity arose. Hence information on the different effects of different stockings was not available. Therefore, no distinction was made on the differences between types of stockings including above and below knee stockings. In addition, no recommendations could be made on the strength of compression hosiery as defined by its class (class I, II or III) depending on the strength. The GDG noted that there was a variation in practice with regards to the length and class of stocking prescribed. The GDG wanted to highlight that if a decision to prescribe compression hosiery is made the following aspects should be considered: • The patient should be assessed prior to prescribing hosiery. This should include assessment of peripheral circulation, dexterity and severity of symptoms. In addition, accurate measurement of the leg is important to ensure a good fit. • The hosiery should be fitted correctly and, where appropriate, aids for the application of hosiery should be prescribed. • Advice and training should be given about how to put them on, when to wear them and how to look after them, as well as information on regular clinical follow-up and what signs are indicators for seeking medical help.

	• Patients can be advised that in most instances they are able to return to work whilst wearing compression bandaging or hosiery. • Compliance with hosiery is an important consideration as the effectiveness of this treatment is dependent on it being worn. **Key priority for implementation** The recommendation was identified as a key priority for implementation. The GDG prioritised it as it has a high impact on reducing variation in care and will lead to more efficient use of NHS resources. There is a variation in the country regarding the prescription of compression hosiery and the cost effectiveness model (section 9.6) identified that interventional treatment was more cost effective than compression therapy. **Research Recommendation** • **What is the clinical and cost effectiveness of compression hosiery versus no compression for the management of symptomatic varicose veins?** The GDG considered that the small benefits in some of the patient reported symptoms and the reductions in complaints was enough to recommend a trial of compression hosiery and have made a future research recommendation to investigate the clinical and cost effectiveness of compression hosiery versus no compression for the management of symptomatic varicose veins. It was accepted that further research is urgently needed to clarify effectiveness and as such the research was chosen as a top future recommendation for research. The GDG highlighted that barriers to adherence should be taken into account as part of the research, as should the length and compression profile of the hosiery. Further details of the research is detailed in appendix N.

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10 Compression post interventional treatment

10.1 Review Question: What is the clinical and cost effectiveness of interventional treatment followed by compression compared with interventional treatment alone in people with leg varicose veins, and, if so, what type of compression, pressure of compression and/or duration of compression is optimal?

For full details see review protocol in appendix C.

Table 83: PICO characteristics of review question

Population	Adults with leg varicose veins
Intervention/s	Stripping surgery immediately followed by compression OR Avulsion surgery immediately followed by compression OR Endothermal ablation immediately followed by compression OR Foam sclerotherapy immediately followed by compression
Comparison/s	For the first part of the review question, the comparator in each case will be as the intervention, but without compression as an adjunct. For the second part of the review question, the comparator will be as the intervention but adjunctive compression will vary in terms of: • another type of compression (i.e. bandaging) • a different compression pressure • a different duration of treatment
Outcomes	• Patient-reported outcome:- ○ Health-related quality of life ○ Patient-assessed symptoms. • Physician-reported outcomes. • Presence of reflux • Need for additional/further treatment • Adverse events from intervention • Prevention of complications from varicose veins • Return to work / normal activities
Study design	Systematic reviews, RCTs

10.1.1 Clinical evidence

For the first part of the review question (What is the clinical and cost effectiveness of interventional treatment followed by compression compared with interventional treatment alone in people with leg varicose veins) we searched for randomised controlled trials comparing the effectiveness of:

- Surgery / endothermal ablation / foam sclerotherapy combined with compression therapy with
- The corresponding interventional therapy applied alone.

2 RCTs were found that made the above comparison. One compared foam sclerotherapy plus compression versus foam sclerotherapy alone (Hamel-Desnos 2010[38]). Houtermans-Auckel 2009[41] compared the extended use of compression treatment after stripping surgery . They used elastic bandages for both arms of the study over the first 3 days post-surgery, as per routine practice, and an additional 4 weeks of compression stocking in the intervention arm. Since the review question was strictly concerned with the comparison between intervention followed by compression and intervention alone, the outcomes from this paper were downgraded for indirectness as ideally the intervention group would have received full compression immediately post-surgery.

Evidence from these are summarised in the clinical GRADE evidence profile below (Compression vs no compression after stripping surgery

Table 85). See also the study selection flow chart in appendix D, forest plots in appendix I, clinical evidence tables in appendix G and exclusion list in appendix J.

Table 84: Summary of studies included in the review

Study	n	CEAP grades	Age (Intervention/ control)	Intervention details	Comparator	Follow-up
Houtermans-Auckel 2009[41]	104	C2-3	49/50	Stripping (spinal anaesthetic) PLUS 3 days of elastic bandages plus 23-32 mmHg stockings for 4 weeks	Stripping (spinal anaesthetic). 3 days of elastic bandages only.	4 weeks
Hamel-Desnos 2010[38]	60	C2-6	53/61	Foam sclerotherapy PLUS 15-20 mmHg stockings for 3 weeks	Foam sclerotherapy. No compression applied	4 weeks

10.1.1.1 Compression vs no compression after stripping surgery

Table 85: Clinical evidence profile (GRADE table): surgery plus compression vs surgery alone for varicose veins

Quality assessment							Summary of findings				
							Meta-analysis result for dichotomous variables; individual study results for continuous variables.		Effect		Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery with comp Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	surgery alone Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Relative (95% CI)	Absolute	
Adverse events – Post-operative pain – 2 weeks (Better indicated by lower values)											
1 Houtermans-Auckel 2009[41]	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	2.2(2.3)[46]	2.2(2.4)[50]	-	MD 0 higher (0.94 lower to 0.94 higher)	VERY LOW
Adverse events – Post-operative pain – 4 weeks (Better indicated by lower values)											
1 Houtermans-Auckel 2009[41]	randomised trials	very serious[a]	no serious inconsistency	serious[b]	Serious[c]	none	0.8(1.5)[46]	0.5(0.8)[50]	-	MD 0.3 higher (0.19 lower to 0.79 higher)	VERY LOW
Adverse events – Numbness – 2 weeks											
1 Houtermans-Auckel 2009[41]	randomised trials	very serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	0/46 (0%)	2/50 (4%)	RR 0.22 (0.01 to 4.4)	31 fewer per 1000 (from 40 fewer to 136 more)	VERY LOW

Adverse events – Numbness – 4 weeks											
1 Houtermans-Auckel 2009[41]	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	0/46 (0%)	0/50 (0%)	not pooled	not pooled	VERY LOW
Return to work (days) (Better indicated by lower values)											
1 Houtermans-Auckel 2009[41]	randomised trials	very serious[a]	no serious inconsistency	serious[b]	Serious[c]	none	15(8.4)[46]	11(7.5)[50]	-	MD 4 higher (0.8 to 7.2 higher)	VERY LOW

(a) Outcomes were downgraded by two levels for limitations because of at least two of the following: lack of allocation concealment, lack of blinding and lack of attrition bias

(b) Outcomes were downgraded by one level if the degree of inconsistency across studies was deemed serious (I squared 50–74%).

(c) Outcomes were downgraded by two levels if the degree of inconsistency was deemed very serious (I squared 75% or more). Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

10.1.1.2 Compression vs. no compression: foam sclerotherapy

Table 86: GRADE assessment for the comparison of foam sclerotherapy plus compression versus foam sclerotherapy alone for varicose veins

Quality assessment							Summary of findings				
							Meta-analysis result for dichotomous variables; individual study results for continuous variables.		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Foam sclerotherapy with compression Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Foam sclerotherapy alone Mean (sd) [n] OR median (IQR) [n] OR frequency (%)	Relative (95% CI)	Absolute	
QoL - CIVIQ global - change from baseline - 14 days (Better indicated by more negative values)											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	-5.5(10)[22]	-9(9.9)[21]	-	MD 3.5 higher (2.45 lower to 9.45 higher)	VERY LOW
QoL - CIVIQ global - change from baseline - 28 days (Better indicated by more negative values)											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	-9.4(10)[23]	-11(14)[24]	-	MD 1.6 higher (5.33 lower to 8.53 higher)	VERY LOW
Reflux at 28 days											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/31 (0%)	0/29 (0%)	not pooled	not pooled	LOW

Adverse events - major neurological events											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/31 (0%)	0/29 (0%)	not pooled	not pooled	LOW
Adverse events - visual disturbance (scotoma) resolving within 15 minutes											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/31 (0%)	1/29 (3.4%)	RR 0.31 (0.01 to 7.38)	24 fewer per 1000 (from 34 fewer to 220 more)	VERY LOW
Adverse events - moderate pain day 28											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/30 (3.3%)	3/29 (10.3%)	RR 0.32 (0.04 to 2.92)	70 fewer per 1000 (from 99 fewer to 199 more)	VERY LOW
Adverse events – pigmentation											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/30 (6.7%)	1/29 (3.4%)	RR 1.93 (0.19 to 20.18)	32 more per 1000 (from 28 fewer to 661 more)	VERY LOW
Adverse events – thrombophlebitis											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/30 (10%)	3/29 (10.3%)	RR 0.97 (0.21 to 4.41)	3 fewer per 1000 (from 82 fewer to 353 more)	VERY LOW
Patient assessed symptoms - heavy legs											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	20/30 (66.7%)	16/29 (55.2%)	RR 1.21 (0.8 to 1.83)	116 more per 1000 (from 110 fewer to 458 more)	VERY LOW

Patient assessed symptoms – pain											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	21/30 (70%)	17/29 (58.6%)	RR 1.19 (0.81 to 1.76)	111 more per 1000 (from 111 fewer to 446 more)	VERY LOW
Patient assessed symptoms – oedema											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	15/30 (50%)	15/29 (51.7%)	RR 0.97 (0.59 to 1.6)	16 fewer per 1000 (from 212 fewer to 310 more)	VERY LOW
Patient assessed symptoms – paraesthesia											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	17/30 (56.7%)	13/29 (44.8%)	RR 1.26 (0.76 to 2.11)	117 more per 1000 (from 108 fewer to 498 more)	VERY LOW
Patient assessed symptoms – cramp											
1 Hamel-Desnos 2010[38]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	11/30 (36.7%)	16/29 (55.2%)	RR 0.66 (0.37 to 1.18)	188 fewer per 1000 (from 348 fewer to 99 more)	VERY LOW

(a) Outcomes were downgraded by two levels for limitations because of at least two of the following: lack of allocation concealment, lack of blinding and lack of attrition bias.

(b) Outcomes were downgraded by one level if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two levels if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables. For continuous variables analysed with the standardised mean difference option, the MIDs were set half a standard deviation either side of the null line.

10.1.1.3 Narrative summary for surgery plus compression versus surgery alone (for outcomes not appropriate for GRADE)

Compliance

Hamel-Desnos 2010[38] reported compliance with compression post-surgery as 12/30 at 28 days (defined as those wearing the hosiery every day).

10.1.2 Economic evidence

10.1.2.1 Published literature

No relevant economic evaluations comparing interventional treatment followed by compression with interventional treatment alone were found.

10.1.2.2 New cost-effectiveness analysis

New analysis was not prioritised for this question.

10.1.2.3 Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below in Table 87 and Table 88 to aid consideration of cost effectiveness.

Table 87: Types of compression hosiery and unit costs

Item	Cost			
	Standard compression stockings		Made-to-measure compression stockings	
	Below-knee	Thigh-high	Below-knee	Thigh-high
Class I compression stockings	£7.21	£7.89	£26.46	£42.30
Class II compression stockings	£10.54	£11.73	£26.46	£42.30
Class III compression stockings	£11.95	£13.90	£26.46	£42.30

Source: NHS Business Services Authority 2011 [70]

Table 88: Resource use and associated costs for compression therapy

Item	Unit cost	Quantity per year	Total cost per year (unit cost * quantity per year)	Notes
Nurse time	£82 per hour	10 minutes	£14	Per hour cost of band 5 nurse patient contact time
Compression stockings/hosiery	£42	4	£168	Price of a pair of thigh-high "made-to-measure" compression stockings. The same price applies to class I, class II and class III compression stockings.
Total			**£182**	

Source: NHS Drug tariff[70]*,PSSRU*[20]

10.1.2.4 Economic considerations

Based on the figures provided in Table 88, it is estimated that the cost of post intervention compression would be approximately £182. This estimate is based on the assumptions that patients are given four pairs of "made-to-measure" thigh-high stockings, and that ten minutes of nurse time is required for the patient to be measured and fitted with stockings. Compression stockings are

assumed to last approximately three months, therefore patients are given two pairs per 6 month period.

In practice, some people may be given below-knee standard compression stockings instead of thigh-high "made-to-measure" stockings. If below-knee standard compression stockings are prescribed it is estimated (assuming the average price of a pair of standard below-knee compression stockings is £10.54) that the annual costs of compression therapy would be roughly £55.

In order for post intervention compression hosiery to be cost effective, the additional cost would have to be justified by an increase in quality of life. The clinical evidence revealed no clinically important improvement in quality of life from prolonged compression post intervention.

10.1.3 Evidence statements

10.1.3.1 Clinical

10.1.3.1.1 Surgery plus compression versus surgery alone

Adverse events

Post-operative pain at 3 days

- *2 week follow-up:* 1 study comprising 96 participants showed no discernible difference in post-operative pain at 2 weeks between surgery combined with compression and surgery alone [VERY LOW QUALITY].
- *4 weeks follow-up:* 1 study comprising 96 participants showed that surgery combined with compression was associated with more pain at 4 weeks compared to surgery alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Post-operative numbness

- *2 week follow-up:* 1 study comprising 96 participants showed that surgery combined with compression was associated with a lower proportion of participants with numbness at 2 weeks compared to surgery alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].
- *4 weeks follow-up:* 1 study comprising 96 participants showed no numbness in either group and therefore effects were not estimable.

Return to work

- 1 study comprising 96 participants showed that surgery combined with compression was associated with a longer return to work time compared to surgery alone. However this was not a large enough effect to show a clearly appreciable clinical benefit of using surgery [VERY LOW QUALITY].

10.1.3.1.2 Foam sclerotherapy plus compression versus foam sclerotherapy alone

Quality of life –

CIVIQ global score – change from baseline (more negative change is better)

- *14 days follow-up:* 1 study comprising 43 participants showed that foam sclerotherapy combined with compression was associated with a lower improvement in quality of life rating at 14 days compared to foam sclerotherapy alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

- *28 days follow-up:* 1 study comprising 47 participants showed that foam sclerotherapy combined with compression was associated with a slightly lower improvement in quality of life rating at 28 days compared to foam sclerotherapy alone, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Reflux at 28 days

- 1 study comprising 60 participants showed no reflux in either group and therefore effects were not estimable.

Adverse events

Major neurological events

- 1 study comprising 60 participants showed no major neurological events in either group and therefore effects were not estimable.

Visual disturbance (scotoma) resolving within 15 minutes

- 1 study comprising 60 participants showed that foam sclerotherapy combined with compression was associated with a lower proportion of participants with visual disturbance compared to foam sclerotherapy alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Moderate pain day 28

- 1 study comprising 59 participants showed that foam sclerotherapy combined with compression was associated with a lower proportion of participants with moderate pain at day 28 compared to foam sclerotherapy alone, but the uncertainty of this effect is too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Pigmentation day 28

- 1 study comprising 59 participants showed that foam sclerotherapy combined with compression was associated with a greater proportion of participants with pigmentation compared to foam sclerotherapy alone, but the uncertainty of this effect is far too large from which to draw clear conclusions about relative benefit and harm [VERY LOW QUALITY].

Thrombophlebitis

- 1 study comprising 59 participants showed no discernible difference in thrombophlebitis between foam sclerotherapy combined with compression and foam sclerotherapy alone [VERY LOW QUALITY].

10.1.3.2 Economic

- No relevant economic evidence was identified
- Compression hosiery post intervention is estimated to cost an additional £182, yet prolonged compression post intervention was not found to be associated with a clinically important improvement in quality of life.

Second part of the review question

However because there was no strong evidence suggesting the clinical efficacy of compression as an adjuvant to interventional therapies, the second part of the review question was not completed.

10.2 Recommendations and link to the evidence

Recommendations	**11. Do not offer compression bandaging or hosiery for more than 7 days after completion of interventional treatment for varicose veins.**
Research Recommendation	**8. What is the clinical and cost effectiveness of compression hosiery after interventional treatment for varicose veins compared with no compression hosiery? If there is a benefit, how long should compression hosiery be worn for?**
Relative values of different outcomes	Health related quality of life was considered the most important outcome for this comparison. Patient reported relief from symptoms associated with chronic venous insufficiency was also considered an important outcome. This included pain, ankle swelling, cramps and the feeling of having tired / heavy legs.
Trade off between clinical benefits and harms	There was an absence of evidence and only one study comparing foam sclerotherapy and foam sclerotherapy alone was identified. No important differences were noted in health related quality of life or in any reported patient reported outcomes for foam sclerotherapy with compression compared with foam sclerotherapy alone. There appeared to be an important disadvantage of surgery with compression in terms of a slower return to work compared with surgery alone. There was little evidence of any difference for any other outcome reported. The potential benefits of compression after interventional treatment need to be balanced against the potential costs of compression and any harm (such as comfort for the patient).
Economic considerations	No economic studies were identified. Costs of compression therapy were estimated using the cost of 4 compression stockings/hosiery per year and a band 5 nurse time. Based on these calculations the cost of post intervention compression would be approximately £182. As clinical evidence revealed little improvement in quality of life from prolonged compression post intervention, compression post intervention was not expected to be cost effective compared to no prolonged compression.
Quality of evidence	Two studies were included in the clinical evidence. One study compared foam sclerotherapy with compression for one month with foam sclerotherapy alone. One study compared compression after surgery with surgery alone. All patients in this study had compression for three days after surgery. At this point patients were randomised to 4 weeks further compression or no compression. For both studies the outcomes were of low or very low quality, with both studies being prone to serious bias and some being affected by imprecision. In most cases the imprecision of the point estimate was too large to be able to confidently judge the magnitude/direction of the true population effect.
Other considerations	The recommendation was based on the limited evidence which had a quality of low to low evidence, and GDG consensus. The GDG discussed the evidence and noted that no neurological events were recorded with the use of stockings. As there was no convincing evidence for using or not using compression therapy the GDG felt they could not make a recommendation not to use stockings at all post operatively and the consensus was that in their clinical experience some people post-surgery did feel benefit from wearing stockings. However the GDG, taking into account the cost of compression therapy, felt they could not recommend its long term use. Patients can be advised that in most instances they are able to return to work whilst wearing compression bandaging or hosiery. **Research recommendation** • **What is the clinical and cost effectiveness of compression hosiery after interventional treatment for varicose veins compared with no compression hosiery? If there is a benefit, how long should compression hosiery be worn for?**

	As the clinical evidence available was subject to serious bias and the benefits of compression after treatment were unclear, the GDG recommended a future research recommendation to complete a randomised controlled trial of compression hosiery after interventional treatment for varicose veins. Further details of the proposed research recommendation can be found in appendix N.

1

11 Pregnancy

It was identified during the scoping stage that as varicose veins are common during pregnancy (affecting about 40% of pregnant women) that this group required additional consideration in the guideline. The management of vulval varicose veins is out of the scope of this guideline.

11.1 Clinical evidence

None of the literature searches completed for the review questions within the guideline excluded pregnancy as a condition. Therefore we can be confident that all the clinical evidence concerning the management of varicose veins during pregnancy is likely to have been identified. This section aims to collate and summarise the findings across different guideline questions to allow recommendations to be made for this group.

The summary below details the literature on pregnant women that was included in the review questions, and also the literature that was not included because of exclusion criteria specific to certain review questions but has information on pregnant women. Evidence tables are available in appendix G

11.1.1 Information and perceptions about varicose veins in relation to pregnancy

Chapter 5 reviews the evidence for the perceptions and expectations of people with varicose veins. Although it is unclear from the evidence how many of the participants were, or had been pregnant, Zubilewicz 2009[107], in a survey of patient knowledge of CVI risk factors, found that 58% of patients identified prior pregnancy as a risk factor. This study was assessed to be of very low quality. The principles of giving accurate information to pregnant women are the same as those found in chapter 5, although the risks should be modified based on their condition.

11.1.2 Pregnancy as a risk factor for the progression of varicose veins

Chapter 6.1 investigated the evidence for risk factors which were associated with an increased chance of progression to more serious varicose veins. Two studies were identified which looked at pregnancy as a risk factor for progression.

Venous Reflux

Fowkes 2001[34] detected a univariate trend for previous pregnancies to be associated with the existence of venous reflux [OR: 1.20 (0.93-1.54)], but this effect disappeared after multivariable analysis [OR: 0.96(0.71-1.29)]. Note that this is not an outcome relevant to progression of varicose veins, as the study was cross-sectional, and there was no measure of any change in severity status. No analysis was undertaken to establish associations between pregnancy and varicosities.

The quality of this outcome was classified as low, downgraded for the lack of assessor blinding and the use of a cross-sectional analysis. This evidence has not been previously included in the guideline as we do not have a review question addressing etiological factors for the incidence of varicosities or reflux; however, this is an important issue in the context of pregnancy.

Progression of varicose veins

Mota Capitao 1995[60] assessed prior pregnancy as a possible risk factor for progression of varicose veins, but after multivariable analysis it was not shown to be a significant risk factor. The quality of this outcome was classified as very low, downgraded for indirectness, use of a cross-sectional methodology, and a lack of blinding of assessors.

11.1.3 Pregnancy as a predictor of treatment outcome

Chapter 6.2 investigated risk factors which predicted a better or worse outcome after interventional treatment. One study was identified which looked at pregnancy.

Fischer 2006[32] assessed previous pregnancy as one of many factors influencing reflux recurrence after great saphenous vein ligation and stripping. After multivariable analysis, prior parity was an independent predictor, leading to a 2.69 fold increase in the odds of reflux recurrence (95% CIs: 1.45-4.97) compared to no parity. Interim pregnancy during follow-up was also an independent predictor of reflux [OR: 4.74(2.47-9.12)]. The quality of these outcomes were classified as moderate, with a single downgrade for the lack of assessor blinding.

11.1.4 Interventions for varicose veins in pregnancy

Chapters 8 and 9 investigate compression and interventional treatment options for the management of varicose veins. All of the studies included in these sections excluded pregnant women.

Thaler 2001[101] evaluated compression stockings as prophylaxis of varicose veins in pregnancy (population of all pregnant women under 12 weeks gestation, with no baseline reflux) compared to no treatment. Compression failed to prevent the emergence of superficial varicose veins, although it did appear to reduce the risk of GSV reflux and worse symptoms in those that already had mild varicose veins at baseline. The quality of the three relevant outcomes from this study were all classified as low, based on a lack of allocation concealment and inadequate blinding. Our reason for excluding this study from the compression compared with no treatment review question (chapter 8) was that prophylaxis was out of the scope of the guideline.

11.1.5 Related NICE guidance

NICE produced a guideline on routine care for the healthy pregnant woman (NICE Antenatal guidelines) in 2008.[63] Within this guideline there was one recommendation for women with varicose veins:

"Women should be informed that varicose veins are a common symptom of pregnancy that will not cause harm and that compression stockings can improve the symptoms but will not prevent varicose veins from emerging."

This recommendation was based on was based on the findings from Thaler 2001[101].

11.1.6 Economic evidence

Published literature

No cost effectiveness evidence was identified for this specific population.

11.1.7 Evidence Statements

11.1.7.1 Clinical

- One low quality study comprising 42 participants showed that compression does not prevent the incidence of varicose veins in pregnant women [LOW QUALITY].
- One low quality study comprising 42 participants showed that compression may decrease the risk of progression of varicose veins in pregnant women [LOW QUALITY].
- One low quality study comprising 42 participants showed that compression may decrease the symptoms from varicose veins in pregnant women [LOW QUALITY].

- One low quality study comprising 739 participants showed that pregnancy does not have an association with the existence of venous reflux [LOW QUALITY].
- One very low quality study comprising 474 participants showed that prior pregnancy does not influence progression of varicose veins [LOW QUALITY].
- One moderate quality study comprising 1261 participants showed that prior pregnancy may increase the risk of reflux recurrence after varicose veins surgery [LOW QUALITY].
- One moderate quality study comprising 1261 participants showed that interim pregnancy at follow-up may increase the risk of reflux recurrence after varicose veins surgery [LOW QUALITY].

11.1.7.2 Economic

- No cost effectiveness evidence was found for this specific population.

11.2 Recommendations and link to evidence

11.2.1 Provision of information

Recommendations	12. Give pregnant women presenting with varicose veins information on the effect of pregnancy on varicose veins.
Relative values of different outcomes	The outcomes used in this review were any reported in the papers reviewed for chapter 5. The GDG considered any reported perceptions and expectations as equally important. The possible adverse events both to the woman and her unborn child were considered by the GDG in their decision making.
Trade off between clinical benefits and harms	No evidence was identified evaluating the perceptions and expectations of pregnant women with varicose veins (chapter 5). The GDG considered that there are few, if any, harms from exploring perceptions and expectations at the initial consultation and by providing accurate information for people with varicose veins. The GDG considered that the clinical benefits of providing information to women with varicose veins during pregnancy did not outweigh the possible harms to the woman and the unborn child.
Economic considerations	It was expected that the impact of providing patient information on time and resource use would be minimal, and would likely be offset by an improvement in quality of life.
Quality of evidence	The quality of the study included in the review is considered to be very low.
Other considerations	On the whole advice given to pregnant women is no different anyone else with varicose veins except the GDG was aware of evidence that indicated that although varicose veins may appear during pregnancy, that there was a chance that these would regress in the postnatal period. This was also their experience clinically and the GDG felt that pregnant women should be made aware of this.

11.2.2 Interventional treatment during pregnancy

Recommendation	**13. Do not carry out interventional treatment for varicose veins during pregnancy other than in exceptional circumstances.**
Research recommendation	**9. How long after giving birth should women wait before having interventional treatment for varicose veins?** **10. Should women have their varicose veins treated 'between' pregnancies or advised to wait until they do not plan to have any more children?**
Relative values of different outcomes	Health related quality of life was considered the most important outcome for this question. Patient reported relief from symptoms associated with chronic venous insufficiency was also considered an important outcome. This included pain, ankle swelling, cramps and the feeling of having tired / heavy legs. The possible adverse events both to the woman and her unborn child were considered by the GDG in their decision making.
Trade off between clinical benefits and harms	The GDG considered that the clinical benefits of interventional treatment for varicose veins during pregnancy did not outweigh the possible harms to the woman and the unborn child. The evidence for this review came from the review of the role of compression (chapter 8) and interventional treatments (chapter 9) in the management of varicose veins. None of the studies included pregnant women.
Economic considerations	The primary concern is safety for the woman and the unborn child; treatment is not advised in pregnant women, therefore cost-effectiveness is not considered.
Quality of evidence	None of the studies included in the intervention reviews included pregnant women.
Other considerations	The GDG commented that due to the lack of evidence and lack of safety information, interventional treatment of varicose veins should not normally be offered to women during pregnancy. However there may be some exceptional situations, for example when a woman has bleeding varicosities, where intervention could be considered. These situations should be referred to a vascular specialist for their assessment of the risks and benefits of interventional treatment. The GDG discussed the length of time after giving birth before varicose veins interventional treatments should be given. There was a general consensus that this should be at least 3-6 months due to normalisation of the body after giving birth and the risk of introducing drugs during breastfeeding. The GDG agreed that they wished to avoid being too specific because of the dearth of evidence. They have included as a future research recommendation to investigate when after pregnancy it was it safe to give interventional treatment for varicose veins. The GDG discussed whether women should have their varicose veins treated 'between' pregnancies or advised to wait until they do not plan to have any more children. They did know of any evidence of why a woman should have to wait until she did not think she would have any more children before having treatment and felt that it was an outdated concept. As there was no evidence the GDG suggested that some research could be completed into this area, although they noted that it was likely that this would be an observational study as a trial would not be a feasible or ethical to complete.

11.2.3 Compression hosiery during pregnancy

Recommendations	14. Consider compression hosiery for symptom relief of leg swelling associated with varicose veins during pregnancy.
Relative values of different outcomes	Health related quality of life was considered the most important outcome for this question. Patient reported relief from symptoms associated with chronic venous insufficiency was also considered an important outcome. This included pain, ankle swelling, cramps and the feeling of having tired / heavy legs. The possible adverse events both to the woman and her unborn child were considered by the GDG in their decision making.
Trade off between clinical benefits and harms	The GDG considered that the clinical benefits of treating varicose veins with compression hosiery during pregnancy may outweigh the possible harms to the woman and the unborn child.
Economic considerations	The GDG believe that the improvements in quality of life from compression therapy are likely to justify the additional cost; therefore compression hosiery is considered to be cost-effective (compared to no treatment) for women during pregnancy.
Quality of evidence	No studies were found for this question which included pregnant women. The GDG noted that there was one study of compression stockings in pregnant women which was excluded from our review of compression vs. no treatment as not all of the women had varicose veins at the start of the study and as such it was a trial of prophylaxis. The NICE antenatal guideline has reviewed this paper in full.
Other considerations	The GDG noted that the Royal College of Obstetricians and Gynaecologists (RCOG) have not produced any guidelines for treating varicose veins during pregnancy. The GDG were aware of the current NICE antenatal guideline which included one recommendation for pregnant women with varicose veins. Although they agreed with the spirit of the recommendation (i.e. that pregnant women should be considered for compression hosiery) they did not agree with the precise wording and did not want to reference it in their recommendations. The GDG highlighted that the same issues as when considering compression in any other populations should be taken into account such as measuring the person's legs and prescribing properly fitting hosiery, providing advice about wearing compression etc. These are discussed in the LETR for chapter 8.

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13 Acronyms and abbreviations

ABI	Ankle brachial index. This is synonymous with ABPI
ABPI	Ankle brachial pressure index
AE	Adverse Events
AVVQ	Aberdeen Varicose Vein Questionnaire.
BMI	Body mass index
CEAP	Clinical, Etiologic, Anatomic and Pathophysiologic – a system of grading the level of varicose veins with reference to the skin appearance, the cause of chronic venous insufficiency, the anatomical location of the affected veins and the pathology involved.
CI	Confidence Interval
CIVIQ	Chronic venous insufficiency questionnaire – a varicose veins-specific quality of life scale
CS	Cross sectional
CVD	chronic venous disease
CVI	chronic venous insufficiency
DVT	Deep vein thrombosis
DVI	Deep venous insufficiency
EQ-5D	EuroQol 5D – a generic quality of life assessment form
EVLA	Endovenous laser ablation
EVRF	Endovenous radiofrequency ablation
FN	False negative
FP	False positive
FU	Follow-up
GA	General Anaesthetic
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSV	Great saphenous vein
HHD	Hand held Doppler
HR	Hazard Ratio
HRQL	Health Related Quality of Life
HVVSS	Homburg Varicose Vein Severity Score. A measure of varicose vein severity based on patient reported symptoms, clinical findings and venous function/dysfunction assessed by the clinician.

IQR	Interquartile Range
ITT	Intention to treat
LA	Laser ablation
LASER	Light amplification by stimulated emission of radiation
LSV	Long saphenous vein – more commonly referred to as the Great Saphenous vein (GSV)
MCS	Medical compression stockings
MD	Mean difference
MID	Minimum important difference. This refers to the smallest difference in a measure that would have a clinically relevant impact upon a patient.
MTP	Mid-thigh perforator
OR	Odds ratio – the ratio of odds of an outcome event across two groups being compared. An odds ratio is defined as the number with the outcome event divided by those without the outcome event.
NSAIDS	Non-steroidal anti-inflammatory drugs
PAD	Peripheral artery disease
PE	Pulmonary embolism
PI	Perforator Incompetence
PIN	Perforate invagination stripping – a surgical technique used to strip superficial veins, such as the GSV.
PICO	Population, Intervention, Comparison, Outcomes (a framework for devising protocols for the systematic review of interventional studies)
PROM	Patient Reported Outcome Measures
PV	Popliteal vein
SF-36	Short form – 36 (a generic quality of life questionnaire)
SQOR-V	Specific quality of life and outcome response – venous. The SQOR-V is a validated patient related quality of life outcome for Chronic Venous Disease.
QoL	Quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomised Controlled Trial
RFA	Radiofrequency ablation
RR	Relative risk (also known as relative risk, which has the same meaning).
RTW	Return to work
Sd	Standard deviation

SE	Standard error
SEPS	Subfascial endoscopic perforator surgery
SFJ	Sapheno-femoral junction
SFV	Sapheno-femoral vein
SPJ	Sapheno-popliteal junction
SSV	small saphenous vein
TN	True negative
TP	True positive
TP	True positive
UGFS	Ultrasound Guided Foam Sclerotherapy
US	ultrasound
VAS	Visual Analogue Scale
VCSS	Venous clinical severity score
VEINES-QOL	Venous insufficiency epidemiological and economic study – a varicose veins-specific quality of life scale

1

14 Glossary

14.1 Methodology terminology

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before and after study	A study design where outcomes are measured before and after an intervention in one group only.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may be used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in

	order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardised instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred,

	other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Gold standard See 'Reference standard'.	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Loss to follow-up	Loss to follow-up describes the number of subjects that were unable to provide follow-up data. These may include patients who were non-compliant with treatment, but may also include those who completed treatment. Loss to follow-up may cause bias if the reasons for the failure to provide follow data is related to the intervention or risk factor. Loss to follow-up may occur even if an ITT approach has been used - according to the ITT approach, patients who are non-compliant with treatment must be included in the analysis, but can only contribute to the analysis if follow-up data has been collected.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariable model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable. Also termed multivariate model.
Multivariable model	A statistical model for analysis of the relationship between two or more

	predictor (independent) variables and the outcome (dependent) variable. Also termed multivariable model, which is the preferred term.
Negative predictive value (NPV) [In screening/diagnostic tests:]	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: True negative cases/ (true negative cases + false negative cases).
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest. This can be calculated as the reciprocal of the absolute difference in risk of the event between groups.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: true positive cases/(true positive cases + false positive cases)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Power (statistical)	The ability to demonstrate an association when one exists. Power is

	related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus to reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B; the risk of an event is the number of events / (number of events + number of non-events)). Also known as risk ratio.
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B; the risk of an event is the number of events / (number of events + number of non-events)). Also known as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects (true positive cases/ (true positive cases + false negative cases). See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter

	is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases (true negative cases/ (true negative cases + false positive cases). See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Symptomatic	Exhibiting or involving symptoms
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

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14.2 Varicose Veins terminology

ablation	The removal of tissue
ambulatory phlebectomy	A surgical technique to remove superficial varicosities, usually involving an instrument that pierces the skin adjacent to the varicosity, hooks under it, and pulls the varicosity from the skin. Also known as avulsion, hook avulsion, or phlebectomy
Ankle brachial pressure index	The ankle brachial pressure index (ABPI or ABI) is a method for measuring the severity of arterial occlusion in the leg, with a lower score indicating higher severity. Peripheral arterial disease (PAD) is indicated if the ABPI is less than 0.95. Compression is normally contra-indicated if the ABPI is less than 0.8, and should be applied with caution if the ABPI is between 0.8 and 1.
atrophy blanche	Whitened and irregular patches of skin
avulsion	A surgical technique to remove superficial varicosities, usually involving an instrument that pierces the skin adjacent to the varicosity, hooks underneath it, and then pulls the varicosity from the skin. Also known as hook avulsion, phlebectomy, or ambulatory phlebectomy
bilateral	Both legs affected
CEAP classification	Clinical, Etiologic, Anatomic and Pathophysiologic – a system of grading the level of varicose veins with reference to the skin appearance, the cause of chronic venous insufficiency, the anatomical location of the affected veins and the pathology involved.
C0	CEAP Classification of CVI: skin with no visible signs of varicose veins or thread veins
C1	CEAP Classification of CVI: skin with thread veins visible
C2	CEAP Classification of CVI: skin with varicose veins visible
C3	CEAP Classification of CVI: visible oedema secondary to CVI
C4	CEAP Classification of CVI: skin showing skin changes such as pigmentation, eczema, lipodermatosclerosis or atrophy blanche
C4a	CEAP Classification of CVI: skin showing skin changes such as pigmentation or eczema,
C4b	CEAP Classification of CVI: skin showing skin changes such as lipodermatosclerosis or atrophy blanche
C5	CEAP Classification of CVI: skin with healed venous ulcers
C6	CEAP Classification of CVI: skin with active venous ulcers
Chronic venous disease	The full range of anatomical and functional venous system disorders
Chronic venous insufficiency	The condition where veins cannot return blood to the heart effectively
compression	The application of pressure to the tissues of the lower leg to artificially increase venous return; this is usually achieved with elastic stockings or

	bandages
Compression bandaging	The application of pressure to the tissues of the lower leg via bandages to artificially increase venous return.
Compression hosiery	Elastic stockings to increase venous return; these can be made to measure the patient, and come in different pressures.
Compression stockings	Synonymous with compression hosiery
Compression therapy	Therapy involving the application of pressure to the tissues of the lower leg to artificially increase venous return; this includes elastic stockings or hosiery, bandages or intermittent pneumatic devices.
continuous wave Doppler	A device utilising Doppler ultrasound that permits visualisation of blood flow in the superficial deep veins. Also known as hand held Doppler
Crossectomy	Division of a truncal vein and ligation of tributaries
deep veins	The veins located most deeply in the limb, such as the common femoral vein
dermatitis	Skin inflammation, often characterised by redness, swelling, itching and lesions
Doppler ultrasound	In the context of varicose veins, this is ultrasound that provides imaging of a vein, while also providing colour-coded information on the speed and direction of blood flow.
Duplex	A device utilising Doppler ultrasound that permits accurate visualisation of blood flow in the superficial, perforating and deep veins.
Endothermal	A specialised form of endovenous treatment that ablates via thermal damage to the inner lumen of the vein.
Endovenous	Within the vein; usually applied as a prefix to therapies such as sclerotherapy, laser ablation or radiofrequency ablation that work by ablating and sclerosing the inner lumen of the vein.
flush ligation	Ligation of the short or long saphenous veins, flush with the deep veins into which they drain
foam sclerotherapy	Sclerotherapy using a sclerosant that has been mixed with a gas to make a foam
hand held Doppler	A device utilising Doppler ultrasound that permits insonation of the blood to allow assessment of flow in the superficial deep veins. Also known as continuous wave Doppler
hook avulsion	A surgical technique to remove superficial varicosities, usually involving an instrument that pierces the skin adjacent to the varicosity, hooks under it, and pulls the varicosity from the skin. Also known as avulsion, phlebectomy, or ambulatory phlebectomy
hyperpigmentation	Darkening of an area of skin
laser ablation	An endothermal ablation technique that uses laser energy to cause venous ablation and closure by raising the temperature of the inner lumen of the vein

Ligation	A surgical technique where veins are tied off proximally; this usually results in atrophy of the vein
lipodermatosclerosis	A skin change consisting of hardening of subcutaneous fat leading to a flat pitted area
liquid sclerotherapy	Sclerotherapy using a liquid sclerosant
multiparity	the state of having more than 1 child
negative predictive value	The probability that someone with a negative test on the index measure will have a negative test on the gold standard measure
occlusion	the closing or ablation of a vein by endovenous treatments
Patient reported outcome measures	Measures of a patient's health status or health-related quality of life. They are typically short, self-completed questionnaires, which measure the patients' health status or health related quality of life at a single point in time.
perforator veins	The veins linking the superficial and deep veins
phlebectomy	A surgical technique to remove superficial varicosities, usually involving an instrument that pierces the skin adjacent to the varicosity, hooks under it, and pulls the varicosity from the skin. Also known as avulsion, hook avulsion, or ambulatory phlebectomy
pigmentation	skin discolouration
positive predictive value	The probability that someone with a positive test on the index measure will have a positive test on the gold standard measure
pruritis	An itching sensation, often accompanied by scratching
radiofrequency ablation	An endothermal ablation technique that uses radio wave electromagnetic energy to cause venous ablation and closure by raising the temperature of the inner lumen of the vein
recanalisation	the reopening of veins previously closed by endovenous treatments
reflux	the backflow of blood through a venous valve
reticular veins	Intradermal venules of 1-3mm
sclerosing agent	Chemical substances that can cause sclerosis of truncal or tributary veins. Common ones are Polidocanol and Sodium Tetradecyl Sulfate.
sclerotherapy	The injection of chemical substances into a truncal or tributary vein, that causes closure of the vein.
sensitivity	The probability that someone with a positive test on the gold standard measure of a diagnosis will have a positive test on the index measure
specificity	The probability that someone with a negative test on the gold standard measure of a diagnosis will have a negative test on the index measure
spider veins	Intradermal venules of <1mm, also known as telangiectasia or thread veins

stripping	A surgical technique of truncal vein removal, where the vein is stripped from surrounding tissues and removed.
superficial veins	Truncal and tributary veins located nearest to the skin, such as the great saphenous vein
Superficial thrombophlebitis	Inflammation of a vein due to a blood clot in a vein located just below the skin's surface
Symptomatic varicose vein	A dilated, twisted superficial tributary vein that is associated with localised symptoms such as pain, limb heaviness, cramping, burning, swelling or itchiness.
Telangiectasia	Intradermal venules of <1mm, also known as spider veins or thread veins
thread veins	Intradermal venules of <1mm, also known as spider veins or telangiectasia
Ulceration	the development of areas of full thickness skin breakdown
Ulcer	A break on the skin
ultrasound guided sclerotherapy	the injection of a sclerosing agent into a vein guided by real-time ultrasound imaging
unilateral	Only one leg affected
varicose veins	Visible distended superficial veins with venous incompetence.
varicosity	A synonym for varicose veins
varicosis	A synonym for varicose veins
Vascular service	A team of healthcare professionals who can undertake a full clinical and duplex Doppler ultrasound assessment and provide a full range of treatment for vascular problems.
venous ulcer	A break in the skin secondary to CVI

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Appendices

Full appendices are in separate documents

Appendix A – Scope

Appendix B – Declarations of interest

Appendix C – Review protocols

Appendix D – Clinical article selection flowcharts

Appendix E – Economic article selection flowcharts

Appendix F – Literature search strategies

Appendix G – Clinical evidence tables

Appendix H – Economic evidence tables

Appendix I – Forest plots

Appendix J – Excluded studies - clinical

Appendix K – Excluded studies - economic

Appendix L – Cost effectiveness methods and results

Appendix M – Network analysis code

Appendix N – Research recommendations

Appendix O – References for appendices