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Clinical and cost-effectiveness of methods for managing varicose veins

HTA 10/29/01

Protocol

15 March 2011

1. Title of the project:

What is the clinical and cost effectiveness of different methods of managing varicose veins based upon current evidence?

2. Project lead

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3. Plain English Summary

Varicose veins are enlarged, visibly lumpy knotted veins, usually in the legs. Uncomplicated varicose veins can cause discomfort, aching, heaviness and itching.[1] Complications can include superficial thrombophlebitis, external bleeding, lipodermatosclerosis, eczema and ulceration.[2] Varicose veins is part of chronic venous insufficiency, which is reported to have a substantial negative impact on Health-related Quality of Life (HRQoL).[3] Prevalence of varicose veins in the UK has been reported to be between 20-40% in adult.[4,5,6,7] Reported prevalence in women is in the range of 24 and 32%, with male prevalence rates ranging from 14-19%. The NHS performs over 36,000 surgical procedures per year to treat varicose veins[8], although this figure may be affected by economic considerations.

Traditional treatments for varicose veins involve surgical stripping and ligation, non-foam sclerotherapy or conservative management of symptoms. Surgical stripping has been associated with nerve damage, scars, pain and long post-operative recovery. Traditional surgical procedures have been shown to produce a range of adverse effects such as wound infection, haematoma, lymph leaks, scarring, nerve injury and Deep Vein Thrombosis.[9,10,11,12,13,14] Conventional liquid sclerotherapy is considered faster but less effective than surgical stripping.[15] New minimally invasive treatments offer alternative methods of ablating the vein. These treatments typically involve use of laser, radiofrequency or foam scleroscant. These treatments are now widely used and offer potential benefits such as reduced postoperative downtime, reduced complications, faster recovery, fewer physical limitations, increased HRQoL, is reported to have reduced costs and lower recurrence rates compared to surgical stripping, whilst being equally effective.[16,17,18,19;20;21]

The principal outcomes associated with treatment for varicose veins are symptom relief, symptom severity, quality of life, patient treatment satisfaction, retreatment, and the occurrence of related adverse effects. Recurrence of new varicosities is also considered an important outcome of treatment for varicose veins. Reported recurrence rates for vary widely depending on the nature of the surgical technique performed and method of assessment. Two-year recurrence rates of up to 33% are reported[22,23], with reported 5 year recurrence of 41% rising to up to 70% at over 10 years.[24,25] Surgical procedures for recurrence can therefore place considerable demand on the health services.

Four reviews[26,27,28,29] and a cost-effectiveness analysis[30] have recently been published on this topic. The meta-analysis by Leubke *et al* 2008[26] evaluated RFA alone and that by Jia *et al* 2007[28] evaluated foam sclerotherapy alone. The meta-analyses published by Luebke *et al* 2008[27] and van den Bos *et al* 2009[29] considered all three principal minimally invasive techniques but only included some data from twelve and seven relevant RCTs respectively, with susbtantial duplication of included studies. Large numbers of observational and case series studies were also included in the analyses. However, given that almost twenty RCTs are cited across these reviews and meta-analyses, principally for foam

sclerotherapy[31,32,33,34,35,36,37,1,38,15,39], but also for RFA[40,41,42,43,18,44] and EVLA[45,46,47,21], it is possible that both Luebke *et al* and van den Bos *et al* failed to include relevant trial data. Finally, at least six relevant RCTs published since 2008 have been identified by limited scoping searches for this report and have not been analysed in any previous review.[48,49,50,51,52,53] These include head-to-heads trial of EVLA and both ClosureFast[51] and RFiTT[53] RFA techniques. This proposed work would therefore be analysing new data, as well as applying more inclusive criteria and conducting analyses different from previous reviews. The recently published cost effectiveness analysis by Gohel *et al* 2010[30] uses Great Saphenous Vein (GSV) occlusion as a proxy for clinical outcomes, such as symptoms, recurrence and reoperation rates, and only employs utility data from short-term follow-up. The proposed cost-effectiveness model may therefore reach beyond this and might also employ utility data from more recent RCTs.[48,49,51]

4. Decision problem

4.1 Purpose of the decision to be made

The assessment will address the question: What is the clinical and cost effectiveness of different methods of managing varicose veins based on the evidence?

4.2 Clear definition of the intervention

New minimally invasive methods of managing varicose veins: Endovenous Laser Ablation (EVLA), Ultrasound Guided Foam Sclerotherapy (UGFS), Radiofrequency Ablation (RFA) or Obliteration (RFO), and Transilluminated Phlebectomy.

4.2.1 EVLA

EVLA involves insertion and activation of a laser fibre into the varicose vein. Wavelengths used target deoxygenated haemoglobin and/or water.[54]

4.2.2 UGFS

Sclerotherapy involves injecting the vein with a substance that causes it to collapse and be absorbed into the surrounding tissue.[55] UGFS involves the mixing of air with liquid sclerosing solution to create foam. The foam is injected into the affected vein guided by ultrasound.[54]

4.2.3 RFA

RFA involves insertion of a catheter into the varicose vein. Electrodes at the end of the catheter omit high radiofrequency energy which heats tissue at the site, causing collagen shrinkage, denudation of endothelium and obliteration of the venous lumen.[56] This includes techniques such as VNUS Closure and VNUS ClosureFast[51] and Olympus RFiTT.[53]

4.2.4 Transilluminated Phlebectomy

Transilluminated Phlebectomy offers an alternative to multiple phlebectomies. It involves hydrodissection of the varicosities, transillumination facilitating direct visualization of the varicosities, and varicosity removal using a powered endoscopic tissue dissector.[57]

4.3 Place of the intervention in the treatment pathway(s)

This review will focus on the use of interventions in the treatment of varicose veins.

4.4 Relevant comparators

Any. However, this is most likely to consist of surgical treatment, non-foam sclerotherapy and conservative management. Head-to-head trials comparing the minimally invasive techniques will also be included.

4.4.1 Surgical treatments

Traditional surgical treatment of the greater saphenous vein (GSV) typically involves ligation at the saphenofemoral junction followed by stripping to the knee. Treatment of the short saphenous vein (SSV) typically involves ligation at the saphenopopital junction only.[54]

4.4.2 Non-foam sclerotherapy

Sclerotherapy involves injecting the vein with a substance that causes it to collapse and be absorbed into the surrounding tissue.[55]

4.4.3 Conservative management

Conservative management of varicose veins includes use of compression stockings, elevating the legs, regular exercise.

4.5 Population and relevant sub-groups

Adults aged 16 years or more who are being treated specifically for varicose veins.

4.6 Key factors to be addressed

1. Evaluate the clinical and cost-effectiveness of new minimally invasive techniques compared to other techniques, including traditional surgical techniques, non-foam sclerotherapy and conservative management.

2. Evaluate the safety of new minimally invasive techniques versus surgical techniques, non-foam sclerotherapy and conservative management.

3. Identify any key areas for further research

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the PRISMA statement.[58] English and non-English language studies will be included and there will be no limit by date.

5.1 Population

Adults aged 16 years or more who are being treated specifically for varicose veins. Diagnostic criteria will be recorded, where given.

5.2 Intervention

Ultrasound Guided Foam Sclerotherapy (UGFS), Endovenous Laser Ablation (EVLA) and Radiofrequency Ablation (RFA) or Radiofrequency Obliteration (RFO), and Transilluminated Phlebectomy.

5.3 Comparator

Any form of varicose veins managenment, including traditional surgical stripping/ligation, conservative treatment, phlebectomy or other minimally invasive techniques, such as non-foam sclerotherapy.

5.*4 Settings*

Secondary care

5.5 Outcomes

5.5.1 Clinical outcomes

1. Clinical symptoms, as measured by, for example, the Venous Clinical Severity Score (VCSS) (including pain, oedema, inflammation, hyperpigmentation and lipodermatosclerosis)
2. Recurrence rate (recurrence of varices or occurence of new varices) as distinct from initial treatment episode, usually indicated by neoreflux (on duplex scanning)
3. Early and late re-operations and re-do procedures
4. Post-operative complications, may include but are not limited to, e.g. nerve damage, skin burns, deep venous thermal injury, deep vein thrombosis, pulmonary embolism, transient ischaemic attacks, stroke, bleeding, infection, thrombophlebitis, headache, visual disturbance, skin staining, pain at injection site, back pain, anaphylaxis, lymph leak, cellulitis etc.

5.5.2 Cost and utility outcomes

1. Cost effectiveness and cost utility
2. Quality of Life as measured by, for example, the Aberdeen Varicose Vein Questionnaire (AVVQ) and Short Form 12 (SF-12)

5.6 Follow-up

There is to be no minimum duration of follow-up.

5. 7 Study design

Randomised Controlled Trials (RCTs) only. Scoping searches and an examination of the review literature indicates that there is likely to be more than four or five relevant RCTs for each technique (see section 3, p.2 above) .

5.8 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

5.8.1 Electronic searches

A comprehensive search will be undertaken to identify systematically both clinical and cost-effectiveness literature comparing different methods of the management of varicose veins. The search will involve only combining terms for the population (varicose veins) and the interventions of interest, i.e. the new minimally invasive techniques. This highly sensitive search (i.e. not using terms for comparators, outcomes or study design) is possible because scoping searches using this strategy retrieved relatively small and manageable numbers of citations. An example MEDLINE search strategy is reported in **Appendix 1**. The aim of the strategy is to identify all studies that report on trials or controlled studies comparing new techniques with traditional surgery, non-foam sclerotherapy or conservative management. All searches will be done by an Information Specialist (AC).

5.8.2 Databases

The following electronic databases will be searched from inception for published and unpublished research evidence:

- MEDLINE (Ovid) 1950-;
- EMBASE (Ovid) 1980-;
- CINAHL (EBSCO) 1982-;
- The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, HTA and NHS EED databases 1991-;
- Biological Abstracts (via ISI Web of Science) 1969-;
- Science Citation Index (via ISI Web of Science) 1900-;
- Social Science Citation Index (via ISI Web of Science) 1956-;
- Conference Proceedings Citation Index- Science (CPCI-S)- (via ISI Web of Science) 1990-

- UK Clinical Trials Research Network (UKCRN) and the National Research Register archive (NRR);
- Current Controlled Trials;
- Clinical Trials.gov up;

All citations will be imported into Reference Manager software and duplicates deleted.

5.9 Inclusion criteria

The inclusion criteria are as reported in 5.1-5.7 above. Titles and abstracts of all unique citations will be screened independently by two reviewers using the inclusion criteria outlined below. Disagreement will be resolved by consensus, or with reference to a third team member when necessary. The full papers of all potentially relevant citations will be retrieved so that an in-depth assessment concerning inclusion could be made. Reference-tracking of all included studies and relevant reviews will also be performed to identify additional, relevant studies not retrieved by the search of electronic databases.

5.10 Exclusion criteria

RCTs will be excluded if the focus of the study is the management of a varicose vein complication using the minimally invasive techniques rather than the treatment of varicose veins specifically, i.e. the trial evaluates the management of complications such as ulceration and the principal outcome relates to the complication, eg. leg ulcer healing, rather than the clinical outcomes defined above.

5.11 Data extraction strategy

Data will be extracted from all studies by one reviewer (JL) using a standardised data extraction form piloted on at least one study (see **Appendix 2**). All extractions will be checked thoroughly by a second reviewer (CC). Discrepancies will be resolved by discussion, and with reference to a third team member if necessary.

5.12 Quality assessment strategy

The quality assessment of included RCTs will be undertaken using an appropriate quality assessment criteria. These are included in **Appendix 3**. Critical appraisal will be performed by one reviewer and double-checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third team member if necessary.

5.13 Methods of analysis/synthesis

Data will be tabulated and included studies will be combined in a meta-analysis if the included trials are sufficiently similar in terms of population, intervention, comparator and outcome. Statistical heterogeneity between trials will be accounted for using a random effects meta-analysis and by calculating the I^2 statistic.[59] Binary outcome measures will be analysed assuming a binomial distribution for the observed number of events; continuous outcome measures will be analysed assuming a normal distribution for sample means.

Where trials form a network of evidence in which trials compare one or more different treatments, data will be synthesised using a network meta-analysis to allow a more precise estimate of treatment effect to be calculated and to provide more information with which to estimate the between-study standard deviation. Results will be presented in terms of odds ratios (ORs) and mean difference (MD) for binary and continuous outcome measures respectively.

Absolute estimates of risk and means will be estimated for each treatment by projecting the estimates of treatment effect onto an estimate of baseline risk and an estimate of a baseline mean for binary and continuous outcome measures respectively. The absolute estimates of risk will be used to represent uncertainty about parameters in the economic model.

6. Report methods for synthesising evidence of cost-effectiveness

A systematic review of the existing literature studying the cost-effectiveness of new techniques compared to traditional surgery, non-foam sclerotherapy, and conservative management will be undertaken. In addition, a new economic model will be developed to compare a treatment strategy which incorporates novel techniques with a strategy that uses traditional surgery, non-foam sclerotherapy or conservative treatment.

6.1 Identifying and systematically reviewing published cost effectiveness studies

The search strategy and sources detailed in Section 5 will be used to identify studies of cost effectiveness. The approach described is very sensitive as no study design filters are being used and will retrieve any relevant cost-effectiveness studies. Identified economic literature will be critically appraised and assessed using the Drummond checklist.[60] Existing cost effectiveness analyses will also be used to identify sources of evidence to inform structural modelling assumptions and parameter values for the economic model.

6.2 Development of a health economic model

A *de novo* economic evaluation will be constructed, with the primary outcome from the model being an estimate of the incremental cost per additional quality adjusted life year (QALY) gained associated with use of novel techniques of varicose vein management. The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the condition and potential mortality. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.[61]

The model structure will be determined in consultation with clinical experts. It is expected that a Markov model will be used to follow patient progression following initial treatment into post-treatment health states (reflecting the success or otherwise of treatment and adverse effects of treatment), as well as further recurrences and appearance of new varicosities, although the modelling team have experience in a wide range of different modelling techniques, should these be required following analyses of data.[62,63,64]

Costs will be attached to discrete events (such as treatment of recurrences) as well as ongoing care appropriate to each disease state, allowing lifetime costs to be estimated. Utility values will be associated with each disease/adverse event state to allow total lifetime quality-adjusted-life –years (QALYs) to be calculated. This will allow an analysis of whether novel techniques are more cost effective than traditional surgery, non-foam sclerotherapy or conservative management. Clinical parameters (immediate treatment outcomes, adverse events, recurrence rates) will be taken from the systematic review and meta-analysis of the literature, supplemented by clinical expert opinion where necessary.

Ideally, health related quality of life estimates will be available from the reviewed literature. In the absence of such evidence, the economic model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. National sources (e.g. NHS reference costs[65], national unit costs[66]) as well as the reviewed literature will be used to estimate resource use and costs for use in the economic model.

There will inevitably be some uncertainty around parameter estimates, which will be modelled by the use of appropriate distributions around the central estimates. This will allow probabilistic sensitivity analysis to be undertaken on the model results. Through expected value of perfect information analysis[67] and, if resources allow, expected value of partial perfect information analyses[68] we will identify whether further research is valuable, and in which areas further research is likely to be particularly valuable.

7. Expertise in this TAR team

• **TAR Centre:**

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers in a short timescale, including the National Institute for Health and Clinical Excellence. A list of our publications can be found at:
http://www.sheffield.ac.uk/scharr/sections/heds/collaborations/scharr-tag/reports
Much of this work, together with our reviews for the international Cochrane Collaboration, underpins excellence in healthcare worldwide.

- **Team members' contributions:**

Christopher Carroll, Senior Lecturer in Health Technology Assessment, ScHARR: has extensive experience in systematic reviews of health technologies. CC will lead the project and review of effectiveness. He will co-ordinate the review process, protocol development, abstract assessment for eligibility, quality assessment of trials, data extraction, data entry, data analysis and review development of background information and clinical effectiveness.

Silvia Hummel, Research Fellow, ScHARR : will undertake a review of health economic literature relevant to the study question, as well as design, construct, parameterise, and operate an economic model, and interpret its results.

Joanna Leaviss, Research Associate, ScHARR: will assist CC with the abstract assessment for eligibility, quality assessment of trials, data extraction, data entry and data analysis for the clinical effectiveness review.

Anna Cantrell, Systematic Reviews Information Officer, ScHARR: has experience of undertaking literature searches for the ScHARR Technology Assessment Group systematic reviews and other external projects. AC will be involved in developing the search strategy and undertake the electronic literature searches.

John Stevens: Senior Lecturer in Bayesian statistics in health economics, ScHARR: has extensive experience in the design, analysis and reporting of clinical trials for the pharmaceutical industry, and in the application of Bayesian methods to synthesise data and quantify uncertainty about parameters in economic models. He will advise on and carry out the statistical analyses, including the network meta-analysis.

Matt Stevenson: Reader in health technology assessment, ScHARR: has extensive experience in constructing mathematical models used within health technology assessments. He will provide guidance throughout the project.

Andrea Shippam, Programme Administrator: will assist in the retrieval of papers and in preparing and formatting the report.

- **Clinical and expert advisors:**

Jonathan Michaels, *Professor of Vascular Surgery, University of Sheffield*: has extensive experience of treatment for varicose veins, including experience in leading a large RCT of treatments for the HTA Programme and carrying out systematic reviews for the Cochrane Collaboration.

Dominic Dodd, *Consultant Vascular Surgeon, Sheffield Teaching Hospitals*. Dominic Dodd is recognised as one of the leading endevenous surgeons in the UK and has over fifteen years experience in the treatment of varicose veins. In addition to conventional surgery he has expertise in the use of endovenous laser, radiofequency ablation and scelrotherapy having performed over 1000 endovenous procedures over the last seven years.

8. Competing interests of authors

The authors do not have any competing interests.

The clinical advisors do not have any competing interests. Dominic Dodd is presently a principal investigator in the CLASS trial comparing endovenous laser ablation, foam sclerotherapy and surgery for varicose veins.

9. Timetable/milestones

The project is expected to run from

Milestone	
Draft protocol	31 January 2011
Final protocol	31 March 2011
Start review	30 June 2011
Progress report	30 November 2011
Assessment report	30 December 2011

10. Appendices

1: Draft Medline search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

Search Strategy:

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1 Varicose Veins/ (10432)
2 varicose vein.tw. (854)
3 varicose veins.tw. (4141)
4 vein, varicose.tw. (7)
5 veins, varicose.tw. (17)
6 varices.tw. (9734)
7 varix.tw. (915)
8 varicosis.tw. (381)
9 Saphenous Vein/ (12097)
10 (saphenous adj2 vein$).tw. (10413)
11 (saphena adj2 vein$).tw. (39)
12 or/1-11 (33471)
13 laser ablation.tw. (2406)
14 evla.tw. (54)
15 radiofrequency ablation.tw. (5556)
16 radio frequency ablation.tw. (379)
17 rfa.tw. (1992)
18 foam sclerotherapy.tw. (169)
19 ugfs.tw. (18)
20 illuminated phlebectomy.tw. (0)
21 tipps.tw. (8)
22 or/13-21 (8991)
23 12 and 22 (323)

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Appendix 2: Data extraction forms

Table: Characteristics of included studies

Ref Man ID	**Study** Author, date, country	**Study design**	**Inclusion criteria** (incl. criteria for diagnosis)	**Exclusion criteria** (incl. number excluded)	**Intervention**	**Intervention group characteristics** **N=** 1.Age, gender (f/m) 2.Co-morbidities	**Comparator**	**Comparison group characteristics** **N=** 1.Age, gender (f/m) 2.Co-morbidities

Table: Study outcomes

Ref Man ID	**Study**	**Follow-up**	**Symptoms (I vs C)**	**Numbers with recurrence (I vs C)**	**Numbers needing a second intervention (I vs C)**	**Mortality (I vs C)**	**Adverse events or complications (I vs C)**	**Quality of life** **Cost utilisation**

Appendix 3: RCT Critical Appraisal quality assessment criteria

Trial quality assessment

	Phase III trial
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were the eligibility criteria for study entry specified?	
Were any co-interventions identified that may influence the outcomes for each group?	
Were the outcome assessors blinded to the treatment allocations?	
Were the participants who received the intervention blinded to the treatment allocation?	
Was the success of the blinding procedure assessed?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were the reasons for withdrawal stated?	
Was an intention-to-treat analysis included?	

Y – item addressed; N – no; ? – not enough information or not clear; NA –not applicable

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