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Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial)

JA Michaels, WB Campbell, JE Brazier, JB MacIntyre, SJ Palfreyman, J Ratcliffe and K Rigby

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Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial)

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Abstract

Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial)

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Objectives: To establish the cost-effectiveness of surgery and sclerotherapy for the treatment of varicose veins.
Design: Randomised controlled trials (RCTs) were carried out for conservative treatment, sclerotherapy and surgery for varicose veins. An economic analysis was carried out alongside the randomised trial. Economic modelling was undertaken based on the primary data collection and a literature review (database searches undertaken in April 2000 and updated in March 2001).
Setting: Primary data collection was from a large district general hospital and a teaching hospital both in England over a 2-year period from January 1999. Cost-effectiveness analysis and economic modelling were carried out using an NHS perspective.
Participants: A total of 1009 patients were recruited.
Interventions: Thirty-four patents were randomised in Group 1 (minor varicose veins with no reflux, randomised between conservative treatment and sclerotherapy), 77 in Group 2 (moderate varicose veins with reflux, randomised between surgery and sclerotherapy) and 246 in Group 3 (severe varicose veins with reflux, randomised between conservative treatment and surgery). The remaining 652 patients formed the observational part of the study.
Main outcome measures: The cost-effectiveness analysis was based on NHS treatment costs for the 2002–3 financial year, and utilities based on the Short Form 6D (SF-6D) preference-based health measure. For the clinical trial, the outcome measures were health-related quality of life (HRQoL) [Short Form with 36 Items (SF-36), EuroQol quality of life questionnaire (EQ-5D), visual analogue scale (VAS) and standard gamble], symptomatic relief, anatomical extent (for which a new classification was developed and validated), patient satisfaction and the incidence of complications.
Results: Of the RCTs, only the Group 3 trial was large enough to provide clear results. This showed that surgical treatment produced better results than conservative treatment in terms of HRQoL, symptomatic relief, anatomical extent and patient satisfaction. Clinical outcomes of surgery and sclerotherapy showed significant improvement in the extent of varicose veins, symptomatic and HRQoL parameters. Cost-effectiveness analysis based on the Group 3 trial showed that the surgery produced an estimated discounted benefit of 0.054 quality-adjusted life-year (QALY) over a 2-year period, with an additional discounted cost of £387.45, giving an incremental cost-effectiveness ratio (ICER) of £7175 per QALY. Economic modelling suggested that surgery produced a still greater benefit when considered with a 10-year time horizon, with an ICER of £1936 per QALY. Injection sclerotherapy produced an incremental benefit of approximately 0.044 QALY at a cost of £155 when compared with conservative treatment, giving an ICER of £3500 per QALY. When surgery was compared with sclerotherapy, surgery produced greater benefit with a lower ICER (showing extended dominance).
Conclusions: Standard surgical treatment of varicose veins by saphenofemoral ligation, stripping and multiple phlebectomies is a clinically effective and

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cost-effective treatment for varicose veins, with an ICER well below the threshold normally considered appropriate for the funding of treatments within the NHS. Injection sclerotherapy also appears to be cost-effective, but produces less overall benefit, with a higher ICER than surgery for patients with superficial venous reflux. In minor varicose veins without reflux, sclerotherapy is likely to provide a small average benefit with acceptable cost-effectiveness. Research is needed into methods for accurate and acceptable utility evaluations for conditions with relatively minor effect on HRQoL and also for a validated and standardised method of classification for varicose veins.

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List of abbreviations

AK	above the knee
ANOVA	analysis of variance
BK	below the knee
BMI	body mass index
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DVT	deep vein thrombosis
EQ-5D	EuroQol quality of life questionnaire
FCE	finished consultant episode
HHD	hand-held Doppler
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
LA	local anaesthetic
LSV	long saphenous vein
NICE	National Institute for Health and Clinical Excellence
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REACTIV	Randomised and Economic Assessment of Conservative and Therapeutic Interventions for Varicose Veins (study title)
RR	relative risk
SD	standard deviation
SF-36	Short Form with 36 Items
SF-6D	Short Form 6D
SSV	short saphenous vein
STD	sodium tetradecyl sulphate
SVI	Sheffield Vascular Institute
TTO	time trade-off
VAS	visual analogue scale
VV	varicose vein
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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Executive summary

Objective

The objective of this study was to establish the cost-effectiveness of surgery and sclerotherapy for the treatment of varicose veins.

Design

Randomised controlled trials (RCTs) were carried out for conservative treatment, sclerotherapy and surgery for varicose veins, supplemented by observational data collection in those patients who had exclusion criteria or declined participation in the RCTs. An economic analysis was carried out alongside the randomised trial. Economic modelling was undertaken based on the primary data collection and a literature review (database searches undertaken in April 2000 and updated in March 2001).

Setting

Primary data collection was from two centres, recruiting from sequential referrals of patients with varicose veins to vascular surgeons at a large district general hospital in Exeter and a teaching hospital in Sheffield over a 2-year period from January 1999. Cost-effectiveness analysis and economic modelling were carried out using an NHS perspective.

Participants

A total of 1009 patients were recruited, with 34 being randomised in Group 1 (minor varicose veins with no reflux, randomised between conservative treatment and sclerotherapy), 77 in Group 2 (moderate varicose veins with reflux, randomised between surgery and sclerotherapy) and 246 in Group 3 (severe varicose veins with reflux, randomised between conservative treatment and surgery). The remaining 652 patients formed the observational part of the study.

Main outcome measures

The cost-effectiveness analysis was based on NHS treatment costs for the 2002–3 financial year, and utilities based on the Short Form 6D (SF-6D) preference-based health measure. For the clinical trial, the outcome measures were health-related quality of life (HRQoL) [Short Form with 36 Items (SF-36), EuroQol quality of life questionnaire (EQ-5D), visual analogue scale (VAS) and standard gamble], symptomatic relief, anatomical extent (for which a new classification was developed and validated), patient satisfaction and the incidence of complications.

Results

Of the RCTs, only the Group 3 trial was large enough to provide clear results. This showed that surgical treatment produced better results than conservative treatment in terms of HRQoL, symptomatic relief, anatomical extent and patient satisfaction. The observational study showed no significant differences in outcomes from the RCTs, with no major complications from sclerotherapy and a complication rate of 1.7% following surgery. Clinical outcomes of surgery and sclerotherapy showed significant improvement in the extent of varicose veins, symptomatic and HRQoL parameters.

Cost-effectiveness analysis based on the Group 3 trial showed that the surgery produced an estimated discounted benefit of 0.054 quality-adjusted life-year (QALY) over a 2-year period, with an additional discounted cost of £387.45, giving an incremental cost-effectiveness ratio (ICER) of £7175 per QALY. Economic modelling suggested that surgery produced a still greater benefit when considered with a 10-year time horizon, with an ICER of £1936 per QALY. Injection sclerotherapy produced an incremental benefit of approximately 0.044 QALY at a cost of £155 when compared with conservative treatment, giving an ICER of £3500 per QALY. When surgery was compared with sclerotherapy, surgery produced greater benefit with a lower ICER (showing extended dominance). These findings were robust over a range of univariate and multivariate sensitivity analyses, covering different assumptions, and estimates of probabilities, costs and outcomes.

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Conclusions

Standard surgical treatment of varicose veins by saphenofemoral ligation, stripping and multiple phlebectomies is a clinically effective and cost-effective treatment for varicose veins, with an ICER well below the threshold normally considered appropriate for the funding of treatments within the NHS. Injection sclerotherapy also appears to be cost-effective, but produces less overall benefit, with a higher ICER than surgery for patients with superficial venous reflux. In minor varicose veins without reflux, sclerotherapy is likely to provide a small average benefit with acceptable cost-effectiveness.

Recommendations for further research

One of the key issues in calculating cost-effectiveness is the difficulty in evaluating the potential utility benefit of successful treatment in this condition. Research is needed into the methodology for producing accurate and acceptable utility evaluations for conditions with relatively minor effect on HRQoL. The study demonstrates the difficulty of large RCTs in this area. It is suggested that economic modelling combined with the collection of observational data may provide a useful approach to the assessment of the potential of new treatments for this condition. In future studies, it is important that a validated and standardised method of classification is used to allow comparisons of the extent of varicose veins, the effects of treatment and progression of the disease.

Chapter 1
Introduction

The problem

Varicose veins are very common, affecting 20–40% adults in the UK.[1–4] They pose a huge burden on the NHS: *Table 1* shows the number of procedures from Department of Health figures.[5] In addition to this surgical workload, patients with varicose veins account for large numbers of outpatient attendances in primary and secondary care. Further impact results from a demand for prescription of graduated compression hosiery and treatment of varicose veins by compression sclerotherapy.

The large numbers of patients presenting for treatment (and the larger numbers with varicose veins who might potentially do so) have important implications for the NHS, specifically:

- Logistic implications for the provision of services for assessment and treatment.
- The costs of these services.
- Dilemmas about which patients should have NHS treatment, with 'postcode referral practices' (some NHS Trusts restrict referrals to people with complications such as skin damage, whereas others treat the larger numbers of patients with aching and/or cosmetic complaints).
- Waiting list problems, with their political ramifications. The mean waiting times after being placed on a waiting list for surgery are shown in *Table 1*. In addition, patients usually wait for many weeks or months to be seen in clinic prior to this. Varicose veins are widely perceived as being of low priority; their assessment can be time consuming; and surgery can be lengthy (particularly if veins are recurrent). All of these factors contribute to long waiting times for outpatient clinic appointments and for treatment in many hospitals.
- Specialisation and training. Assessment of varicose veins by surgeons other than vascular specialists, and by their trainees, may result in inappropriate and/or imperfect treatment. This has changed in recent years but may still be an issue in some localities.
- In some patients, varicose veins lead to venous ulceration. This is a chronic condition which places major demands on nursing services and which represents a further massive cost to the NHS.

Aims of the study

The study was known as the REACTIV (Randomised and Economic Assessment of Conservative and Therapeutic Interventions for Varicose Veins) study. The main aim of the REACTIV study was to investigate the clinical and cost-effectiveness of varicose vein treatments.

The central part of the study took the form of randomised controlled trials (RCTs) to compare the most commonly used methods of managing varicose veins. The methods considered in the study were conservative management, injection sclerotherapy and surgery. Since these are appropriate to different patient populations, the study used three separate RCTs on separate groups of patients. Group 1 was those patients in whom there were minor varicose veins in the absence of evidence of reflux in the long saphenous vein (LSV) or short saphenous vein (SSV). These patients were randomised between

TABLE 1 *Procedures done for varicose veins in the NHS in England during 2000–3, including the percentage of patients who were female, the number treated as day cases, the number of bed days used and the average waiting time for treatment*

Year	FCEs[a]	Female (%)	Day cases	Bed days	Waiting time (days)
2000–1	43,432	66.7	22,890	31,429	215
2001–2	40,697	65.3	21,309	29,062	211
2002–3	44,196	65.9	24,025	30,109	216

[a] Finished consultant episodes.

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conservative treatment and sclerotherapy. In Group 2, patients with moderate varicose veins and evidence of reflux were randomised between surgery and sclerotherapy, and in Group 3 patients with more extensive varicose veins in the presence of reflux were randomised between surgery and conservative management.

The study developed a classification for varicose veins to assist in identifying appropriate patients for each group within the study and in assessing progression or recurrence in the follow-up period.

Economic analysis was carried out alongside the RCTs based on cost and resource use data collected within the trials and utility estimates based on health-related quality of life (HRQoL) measures.

Those patients who were excluded or declined participation in the RCTs formed an observational group. Information regarding management, outcomes and follow-up were collected from this group in order to inform economic modelling.

A willingness to pay (WTP) study was carried out to consider aspects of patient preference and economic modelling was undertaken to allow extrapolation of the results and provide further information in areas that were not adequately addressed through primary data collection.

The structure of the report is described at the end of this chapter.

The clinical effects of varicose veins

Cosmetic embarrassment and concern about the future

Most people with varicose veins will suffer no medical harm from them throughout their lifetime. The commonest complaint is their unsightliness, and cosmetic motives probably underlie many requests for treatment on the grounds of minor symptoms. In addition, people are worried about the spectre of complications from their varicose veins – specifically in the context of a family history of ulcers or other leg problems, and also in relation to the risk of deep vein thrombosis (DVT),[6] promoted by recent media reports of the dangers of air travel and venous thromboembolism.

Discomfort

Apart from cosmetic embarrassment and concern about the future, the commonest symptom from varicose veins is discomfort. This can take a variety of forms – typically described by patients as aching, heaviness or itching. These, and other leg pains, are often present in people with varicose veins as a result of other conditions, including arthritis and muscular problems,[7] but a careful history may help to identify symptoms related to varicose veins. Discomfort after prolonged standing, relief by elevation of the leg or by wearing support hosiery and symptoms over the varicose veins may be pointers to a venous cause, but this is an area of uncertainty. Ankle swelling as a result of oedema is another complaint which may result from varicose veins[8] but which has other common causes.

Patients with all these complaints may be said to have 'medically uncomplicated varicose veins' because their veins are causing no damage or threat to their legs: it is in these patients that the greatest uncertainty exists about the benefits and cost-effectiveness of treatment. The 'medical complications' of varicose veins are thrombophlebitis, bleeding, eczema, lipodermatosclerosis (the latter two often conveniently called 'skin changes'), and ulceration.

Superficial thrombophlebitis

This can occur in the absence of varicose veins (when it may be associated with systemic disease such as cancer), but varicose veins are the commonest underlying cause. Treatment of the varicose veins may be considered if they are causing other symptoms or if phlebitis is recurrent (sometimes varicose veins become permanently occluded as a result of phlebitis, and then there is no need to consider definite treatment). Reports of extension of thrombus into the deep veins[9–13] have raised concerns about this risk, but clinical DVT is very uncommon and most cases of superficial thrombophlebitis are dealt with in primary care.

Bleeding

External bleeding is an uncommon consequence of varicose veins and almost always occurs through an area of obviously compromised skin overlying a varicosity in the lower leg. It is alarming and poses a potential threat to life. Bleeding is an indication for early referral and treatment of varicose veins, and this is the recommendation of current guidelines from the National Institute for Health and Clinical Excellence (NICE).[14]

Lipodermatosclerosis and ulceration

The venous hypertension caused by varicose veins is an important cause of damage to the skin and

subcutaneous tissues of the lower leg.[15,16] This usually starts with eczema or pigmentation and may then progress through varying severities of lipodermatosclerosis to ulceration. The chance of any individual with varicose veins developing skin damage is both uncertain[17] and small. Among those who do develop skin changes, the risk of ulceration is also unpredictable, but any signs of venous damage to the skin of the leg is usually regarded as an indication to consider preventative measures – in the form of either compression hosiery or treatment of the varicose veins.

This spectrum of clinical effects means that the impact of varicose veins on HRQoL, the benefit from different kinds of treatment, and the cost-effectiveness of interventions may vary greatly. These considerations have led to local restrictions on the referral of patients to secondary care and geographical inequalities in the provision of varicose vein treatments, with some districts developing local guidance to limit referrals of varicose veins.[18,19]

Assessment of varicose veins

A fundamental aim of examining varicose veins is to identify the sites of valvular incompetence connecting them with the deep veins. Until the mid-1980s it was normal practice for patients simply to be examined clinically and seldom to have any special investigations of their veins. Assessment was by general surgeons, few of whom had a special interest in the management of venous disease, and it was often done by trsinees with limited experience.[20] Since then, practice has changed substantially in a number of respects:

1. **Specialisation.** Surgeons have become increasingly specialised and varicose veins are dealt with largely by vascular surgeons, who have a greater degree of specialist knowledge and interest in their management.[21]
2. **Training.** Trainees can acquire the skills of hand-held Doppler (HHD) assessment fairly rapidly,[22,23] but there is evidence to suggest that trainees are likely to miss the presence of reflux more frequently than fully trained specialists.[24] With increasing numbers of consultants in vascular surgery, more assessment is done or supervised by consultants.
3. **Hand-held Doppler.** HHD has become used increasingly during the last 15 years, based on evidence that it provides more thorough and accurate assessment of reflux in the leg veins[24–29] than traditional examination, including traditional manoeuvres such as the Trendelenberg (tourniquet) test. Most surgeons who use HHD do so as a 'screening test', to select patients for more detailed assessment by duplex ultrasound imaging.[24,29–31] The common criteria for advising duplex are detection of reflux in the popliteal fossa,[32–34] recurrent varicose veins[35] and atypical veins or other uncertainties about the source of reflux into the superficial veins after HHD examination.
   One study by the Exeter group showed that a selective approach to requesting duplex imaging, based on HHD examination, resulted in requests for duplex (or other additional tests) in 60 of 283 (21%) patients.[31] Another study from Leeds showed that duplex imaging would have been requested in 39% of 108 limbs after screening by HHD.[29]
4. **Duplex ultrasound imaging.** This has come to be regarded as the 'gold standard' for assessment of the leg veins, providing both anatomical and haemodynamic information. Studies on the severity[34,36] and distribution[37–39] of reflux detected by duplex scanning have shown some correlation with the clinical state of the limb.
   Some surgeons advocate duplex imaging for all patients presenting with varicose veins[40–44] and this is probably the counsel of perfection. However, availability of vascular technologists' time and of duplex machines is simply not adequate in many hospitals and there is therefore a reasonable argument for using HHD as a screening test, as described above.[24,29,31] This argument depends on knowledge of the accuracy of the clinicians using HHD in detecting reflux that would require correction during treatment of varicose veins.
   Traditional teaching and logic suggest that the more accurate is the assessment of varicose veins (by HHD and by duplex imaging), the more thorough and correct the surgery will be, and as a consequence the more durable the result, but long-term studies have yet to support this view.[45,46] One problem of conducting research into the effectiveness of different methods of assessing and treating varicose veins is the lack of a reproducible method to describe the extent and size of the varicosities (this is dealt with in detail in Chapter 3).
5. **Other special investigations.** These include venography and various forms of plethysmography. They have only ever been used in a minority of patients with varicose veins and have now largely been replaced by

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duplex ultrasound imaging.[35,47–51] They may still have a place in the investigation of patients with varicose veins who also have important deep venous disease.[52–54]

Treatments for varicose veins

The main forms of treatment for varicose veins are conservative treatment, sclerotherapy and surgery – they are described in detail in Chapter 2.

Conservative treatment

Conservative treatment refers to a range of measures which may be pursued by people with varicose veins, either with or without medical advice. Perhaps the most important is simple explanation and reassurance. People with a family history of varicose veins are often frightened that they will 'finish up like their mother', and those with venous ulcers in their family have special concerns. There are widespread misconceptions that varicose veins are associated with a likelihood of DVT, heart disease and amputation. Many people are simply worried that their veins will worsen and cause them harm, so they seek prophylactic treatment.[6] These fears and concerns are not well documented but are familiar to clinicians who regularly see patients with varicose veins and are the subject of an ongoing study in Exeter. They are important reasons why patients presenting with varicose veins require good explanation and reassurance as part of their management, and this element of conservative treatment may be all that is required for many people.

Compression hosiery can be used for relief of symptoms but many patients find this disagreeable and it tends to be used regularly only by those who have troublesome symptoms.

Advice about elevation[55] and exercise is often cited as part of the conservative management of varicose veins, but evidence of effectiveness is lacking and provision of this advice is sporadic.

There are uncertainties about both clinical and cost-effectiveness of conservative measures. They are subject to variation in use by doctors and variable acceptability to patients. In particular, there is no good information about their effect on the quality of people's lives.

Sclerotherapy

Sclerotherapy (compression sclerotherapy or injection treatment) offers a relatively simple form of outpatient treatment which can obliterate varicose veins for a variable length of time. Sclerotherapy became popular in the 1960s[56–58] and dedicated sclerotherapy clinics were established in many hospitals. Since that time, the popularity of sclerotherapy has declined based on evidence of poor long-term effectiveness. Despite its poor long-term results, many patients obtain a satisfactory short-term outcome, sclerotherapy is repeatable and many patients do not return requesting further treatment. Sclerotherapy is now generally considered to be most appropriate for varicose veins below the knee (BK) [where compression is easier to apply than above the knee (AK)] in the absence of saphenous vein reflux. This usually means veins which are not causing severe symptoms or medical complications.

There is almost no published information about the effect of sclerotherapy on HRQoL, its acceptability to patients compared with surgery or its cost-effectiveness. A study by Campbell and colleagues showed that patients preferred the increased chance of a good long-term result from surgery, taking into account the inconvenience and likely discomfort from operation compared with sclerotherapy.[59]

Surgery

Surgery for varicose veins is regarded as the definitive treatment for patients with incompetence in the long or short saphenous trunks.[59–61] The results are longer lasting than those of sclerotherapy,[62–64] but surgical treatment involves a day-case or inpatient operation, general anaesthesia (usually), often a period of recuperation and time off work and the possibility of complications. Recurrence is not uncommon and about 20% patients presenting to hospital with symptomatic varicose veins have had operations before.[25] Recurrence rates ranging from 20 to 80% have been reported between 5 and 20 years after surgery.[65]

The advantages of surgery over other treatments in terms of cost-effectiveness have not been the subject of detailed study. In particular, evidence on the results of surgery compared with other treatments is from the era before ultrasound examination of varicose veins and clinical assessment is known to be frequently flawed.

New endovascular treatments for varicose veins

These include new alternatives to surgical stripping of the long saphenous vein (ablation of the vein by radiofrequency[66–68] or laser[69,70] and

injection of sclerosant foam.[71–73] They have become subjects of debate since the inception of the present project and have not yet disseminated widely in the NHS. The new techniques for ablating the long saphenous vein (radiofrequency or laser) are unlikely to have any important differences in outcome from stripping: they are simply different ways of ablating the long saphenous vein at operation, but controversy surrounds their expense and durability.[74–76]

One other new method recently promoted for use during surgery for varicose veins is transilluminated powered phlebectomy, which is an alternative to hook phlebectomy (avulsion) of varicose veins. This method has its advocates, and it may have advantages for extensive varicosities, but a recent study failed to support its claimed benefits.[77]

None of these treatments was readily available in the NHS at the time when this study was undertaken. They will not be considered further.

Other treatments

For the sake of completeness, it is perhaps worth recording some other treatments which have been used for symptomatic treatment of varicose veins, but which have not entered mainstream practice. Reported drugs used for treatment include dihydroergotamine,[78] flunarizine,[79] rutosides[80] and horse chestnut seed oil.[81] Hydrotherapy with sulphurous water has recently been reported to improve varicose vein symptoms.[82]

Important uncertainties

- How can we be sure which symptoms are being caused by varicose veins?
- What is the effect of varicose veins on HRQoL?
- Which patients will develop medical complications from their varicose veins?
- How should patients be selected for treatment of varicose veins?
- How can assessment of varicose veins be 'standardised' for research purposes?
- What conservative measures are effective in controlling symptoms of varicose veins? What is their cost-effectiveness?
- What is the place of sclerotherapy?
- What are the effects of conservative treatment, sclerotherapy and surgery on symptoms and HRQoL in well-defined groups of patients? How durable are their effects?
- How does the cost-effectiveness of these different treatments compare?

Structure of the report

With a view to addressing uncertainties in the evidence described above, this report presents the work undertaken as follows:

Chapter 2	Review of the existing evidence on • prevalence and epidemiology of varicose veins • treatments for varicose veins (systematic review).
Chapter 3	Description of a new method for classification of the extent and severity of varicose veins.
Chapter 4	Description of clinical trials, including methodology and clinical results.
Chapter 5	Economic analysis of the management of varicose veins, including the economic analysis relating to the clinical trial and a WTP study.
Chapter 6	Economic modelling of the management of varicose veins.
Chapter 7	Discussion and suggested implications of the findings of the various studies for clinical practice and for future research.

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Chapter 2

Review of existing evidence

Prevalence and epidemiology of varicose veins

Determining the prevalence of varicose veins is difficult. Many studies have been published, but they vary in definitions of varicose veins, methods of diagnosis and response rates to questionnaires. They have been undertaken in different countries, on different ethnic groups and on populations of different age ranges and gender distributions. The time when the study was done may have influenced findings and in this chapter only studies published after 1970 have been included.

Tables 2, 3 and *4* show the findings of studies published since 1970, arbitrarily divided between those from 'westernised' societies[1,3,83–92] (*Table 2*), European countries only[1,3,84,87,88,91] (*Table 3*) and various different ethnic groups[93–97] (*Table 4*). Overall, they demonstrate a wide range of observed prevalences. The European data are most relevant to this report and *Table 3* shows these, from studies which specified varicose veins (rather than reticular veins, thread veins, etc.).

Five of the six studies reported prevalences of 24.6–32.2% in women.[1,84,87,88,91] The range in men was wider, but three of five studies which reported male prevalence had results in the range 14.5–19.3%.[1,87,88] The findings of a recent large study from the USA, examining an age-stratified, ethnically mixed population, reported prevalences which fell within these ranges (27.7% in women and 15% in men),[92] as did a similar large study done in the USA in 1973 (25.9% for women and 12.9% for men).[83]

Taking into account all this diverse information, it is reasonable to conclude that the prevalence of visible varicose veins in Europe and the USA is approximately 25–30% for adult women and approximately 15% for men.

Factors affecting prevalence

Gender

All the studies described above which examined gender differences found a higher prevalence in women than men. Just one study reported male predominance, the Edinburgh Vein Study, which is

TABLE 2 *Prevalence of varicose veins in studies reported since 1970 from 'westernised' societies*

First author and year	No. of subjects	Country	Sample population	Age (years)	Prevalence in men (%)	Prevalence in women (%)
Coon, 1973[83]	6389	USA	Random	>10	12.9	25.9
Guberan, 1973[84]	610	Switzerland	Store employees	15–70	–	29
Widmer, 1978[85]	4529	Switzerland	Factory workers	25–74	56 (included reticular veins and thread veins)	55
Abramson, 1981[86]	4802	Israel	Random	>15	10.4	29.5
Novo, 1988[87]	1122	Sicily	Randomised	20–59	19.2	46.2
Leipnitz, 1989[88]	2821	Germany	Random	45–65	14.5	29
Hirai, 1990[89]	541	Japan	Patients and staff	>15	–	45
Franks, 1992[1] (calculated from original report by Evans *et al.*, 1999[4])	1338	England	Random	35–70	17	31
Komsuoglu, 1994[90]	850	Turkey	All local population	>60	34.5	38.3
Sisto, 1995[91]	8000	Finland	Cluster sample from population register	>30	6.8	24.6
Evans, 1998[3]	1566	Scotland	Random?	18–64	39.7	32.2
Criqui, 2003[92]	2211	USA	University employees	40–79	15	27.7

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TABLE 3 *Prevalence of varicose veins in studies of European population samples*

First author and year	No. of subjects	Country	Sample population	Age (years)	Prevalence in men (%)	Prevalence in women (%)
Guberan, 1973[84]	610	Switzerland	Store employees	15–70	–	29
Novo, 1988[87]	1122	Sicily	Random	20–59	19.3	46.2
Leipnitz, 1989[88]	2821	Germany	Random	45–65	14.5	29
Franks, 1992[1] (figures calculated from original report by Evans *et al.*, 1999[4])	1338	England	Random	35–70	17	31
Sisto, 1995[91]	8000	Finland	Cluster sample from population register	>30	6.8	24.6
Evans, 1998[3]	1566	Scotland	Random	18–64	39.7	32.2

TABLE 4 *Selected studies which investigated prevalence in different ethnic groups*

First author and year	No. of subjects	Country	Sample population	Age (years)	Prevalence in men (%)	Prevalence in women (%)
Malhotra, 1972[93]	354	North India	Railway workers	18–65	6.8	–
	323	South India	Railway workers	18–65	25.1	–
Beaglehole, 1975[94]	377	Cook Island	Pukapakans	15–64	2.1	4.0
	417	Cook Island	Rarotongans	15–64	15.6	14.9
	721	New Zealand	Maoris	15–64	33.4	43.7
	356	New Zealand	Europeans		19.6	37.8
	786	Tokleau Island			2.9	0.8
Stanhope, 1975[95]	728	New Guinea	Rural villagers	20–70	5	0.1
Richardson, 1977[96]	1259	Tanzania	Clinic patients	–	4.8	4.1
Maffei, 1986[97]	1755	Brazil	Clinic patients	>15	37.9	50.9

influential because it is a recent and major UK-based population study.[4] The cosmetic aspect of varicose veins is generally more important to women, and all studies which have reported treatment rates describe higher rates for women.[86,91,98]

Age

The prevalence of varicose veins increases with age, as demonstrated in several studies.[4,83,85,86,89,97] Even among children an increased prevalence has been observed between the ages of 10 and 12 years (no varicosities observed) and 14–16 years (observed in 3.7%).[99] In the Edinburgh Vein Study, overall prevalence increased significantly from 11.5% in the age range 18–24 years to 55.7% in the age range 55–64 years.[4]

Ethnicity

Studies in developing countries have generally shown a lower prevalence of varicose veins than those from Europe (see *Table 2*, but note the marked difference in prevalence between railway workers in northern and southern India,[93] those in the south having a prevalence similar to that in Europe). There are, however, no good data on possible variations in prevalence in different racial groups in the UK.

Other factors

It is not the aim of this section to analyse the possible aetiology of varicose veins in detail. However, a variety of factors have been associated with their development, and a brief description of these seems relevant to consideration of their prevalence.

1. **Body mass and height.** Some studies have shown an association between obesity and varicose veins for women,[85,86,100] but this is not a consistent finding.[84,88,89] No such association has been demonstrated for men.[2] A recent report from the Edinburgh Vein Study has shown an association with increasing height for both sexes.[100]

2. **Pregnancy.** Pregnancy appears to increase the risk but any association between numbers of pregnancies and increasing prevalence of varicose veins is controversial.[2] Nevertheless, many women blame pregnancy for the development of their varicose veins.
3. **Family history.** There is a widely held belief of a familial tendency to varicose veins, but people with varicose veins are likely to know of family members also affected by this common condition, so biasing any questionnaire survey towards a positive association.[2] The Edinburgh Vein Study has recently added to the reports of familial susceptibility.[100]
4. **Occupation and lifestyle factors.** There have been reports of increased prevalence among those with occupations which involve prolonged standing,[86,101,102] but these are not conclusive, and the Edinburgh Vein Study failed to show any consistent relationship with lifestyle factors.[100] It is perhaps worth noting that the frequently cited association between the wearing of tight corsets and varicose veins is not supported by convincing evidence.[2,84,86,101]

Key points

- Varicose veins affect 25–30% of adult women and about 15% of men in western society.
- Their prevalence increases with increasing age.
- They are probably more common in women who have been pregnant or who are obese, and there may be a familial susceptibility.

Treatment of varicose veins

Introduction

The published evidence for the treatment of varicose veins is currently poor. A systematic review of injection sclerotherapy has been published in the Cochrane Library,[103] but no other published systematic reviews were available.

In order to evaluate the evidence for treatments for varicose veins, systematic literature reviews were undertaken. All prospective RCTs of treatments for varicose veins were sought. Trials including patients undergoing treatment for the complications of varicose veins (venous ulceration and chronic venous insufficiency) and recurrent varicose veins were excluded. These have been published in the Cochrane Library[104,105] and full details of the search strategies, methodology and results are available in these publications. *Figure 1* shows a breakdown flow diagram of the articles identified for the Cochrane reviews based on the QUOROM statement.[106]

The review process was split into three areas:

- surgery versus sclerotherapy
- stripping of the LSV
- use of a tourniquet.

In addition, other data were identified from existing reviews or other papers relating to the comparison of sclerotherapy and conservative treatment and a range of other treatments.

The search strategy for the review is given in Appendix 1 and the full details will be found in the Cochrane Library. A summary of the results of the review is presented below separately for each of the main areas covered.

Surgery versus sclerotherapy

Seven randomised controlled trials were described in a total of 10 separate papers.[62–64,107–113]

Of the seven studies, only five were directly comparable as they used similar interventions for the surgery and sclerotherapy, namely those by Beresford and colleagues,[109] Doran and colleagues,[110] Einarsson and colleagues,[64] Hobbs[62] and Jakobsen.[63] The two remaining studies compared a new technique for endovascular sclerotherapy against general anaesthetic surgery or local anaesthetic surgery and sclerotherapy, by Belcaro and colleagues,[113] and general anaesthetic surgery with local anaesthetic surgery and sclerotherapy, by Rutgers and Kitslaar.[111]

However, amongst the five comparable studies,[62–64,109,110] there was a wide variation in terms of the outcome measures used in the studies. Consequently, there were insufficient data to perform a meta-analysis. Only one trial, by Einarsson and colleagues,[64] included an objective quantitative measure with which to value the outcome (foot volumetry). The other trials relied on subjective assessment of the results of the interventions. This was probably a result of the widely accepted problem that there are few validated and reproducible outcome measures that can assess the extent or severity of varicose veins. Objective measures such as duplex and foot volumetry could be used but these were not universally employed across the studies. Duplex scanning, however, was not widely available until the 1990s.

The subjective measures used to assess extent and type of varicose veins also were not uniform. Each study made its own classification system and in many cases this system had not been piloted or validated. Direct comparisons between studies were consequently difficult. The second main area

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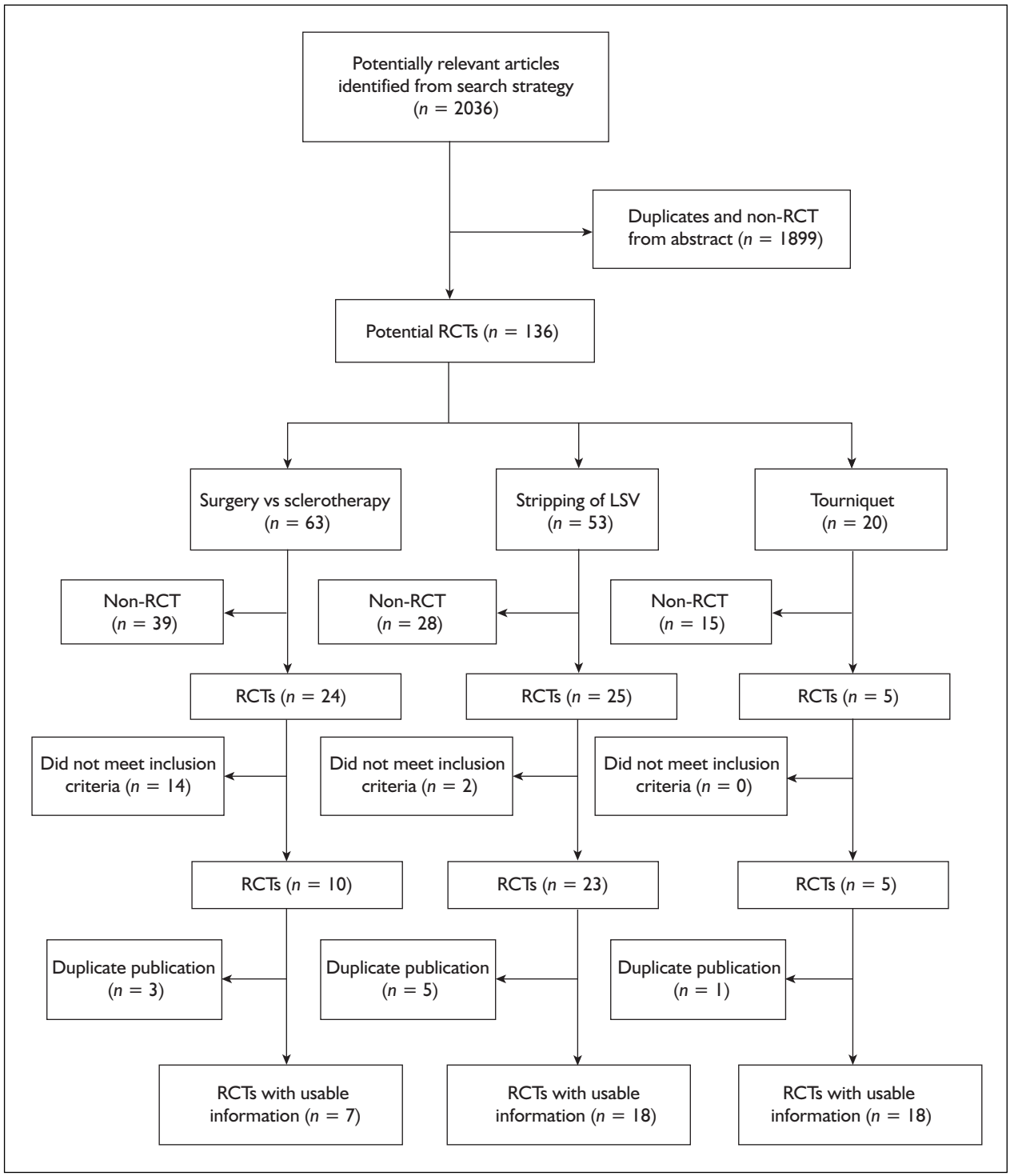

FIGURE 1 *Breakdown of included studies based on QUOROM statement*

of difficulty is the amount of statistical information provided in the trials. Very few provided data that included means, standard deviations (SDs) or confidence intervals (CIs) and some did not even include *p*-values to support their results.

The overall quality of the studies was variable. The main criticism of the studies was that although all seven trials stated that they were randomised, only two, by Einarsson and colleagues[64] and Hobbs,[62] clearly stated their method of randomisation in which the generation of the random sequence and the allocation of the interventions were adequate. This was a major failing, significantly affecting the quality and estimation of treatment effects.[114]

The numbers of patients studied varied between 150 and 516 (mean 261); however, none of the trials had an *a priori* sample size calculation. There were also some discrepancies in the numbers of patients in some of the trials that reported early and late results. In Hobbs's study,[62] the first results were published before the trial had finished recruiting, which may have been a potential source of bias. In Chant and colleagues' trial,[108,109] the initial numbers seen and considered for randomisation were different (339 vs 249), even though the number who were actually randomised was consistent between the two studies. Length of follow-up for the trials was generally good, with a range of 2–10 years (mean 4.86 years).

Many of the measures used were subjective and may not be reproducible or comparable between studies. Only one study[108,109] made any comment on the blinding of their outcome assessor. In some cases blinding of the observers may not have been possible, but in those cases where it was, many of the studies did not clearly state whether they used blinding or not, which again introduces potential bias. Results from statistical methods employed were not clearly documented in a fashion that allowed an accurate assessment of power or precision. All precluded a formal meta-analysis. Even documentation on complication rates, which should have been recorded for all of these trials, was not always provided or given in a standard form. The majority of complications were minor; however, the major ones such as a pulmonary embolism are potentially life threatening. This is a significant risk of treatment for a condition that does not threaten life or limb.

This review highlights many of the problems faced by researchers evaluating treatments for varicose veins. Although the population with varicose veins is large and easily accessible, follow-up can be difficult. In addition, there is a challenge of how to measure change in the state of the varicosities. Subjective measures are always open to bias and no single classification system has been uniformly adopted. Objective measures such as duplex scanning and foot volumetry can be used, but these have not been universally employed in these trials and their relationship with clinical benefit is uncertain.

A general trend to better results after surgery than sclerotherapy was seen in all the trials, but was only consistent when the follow-up period was ≥ 3 years. Of the five comparable trials, three showed that sclerotherapy was more effective in the first year. These outcomes rapidly deteriorated so that by 5 years, surgery was the most effective intervention. For the majority of patients with significant varicose veins, surgery appeared to provide a more long-term benefit than sclerotherapy in terms of recurrence.

When costs were included in the comparison, sclerotherapy had a clear initial advantage, although the data on which costs were based were from the 1960s. Sclerotherapy also appeared to provide benefit in terms of patients not requiring hospital admission or as much time off work. These results were not surprising, but what was not addressed was the true cost-effectiveness of these treatments. In particular, the possible need for repeated treatment by sclerotherapy was not considered. A formal economic cost-effectiveness analysis would be required to address this adequately.

Many of the trials evaluating sclerotherapy were relatively old and there have been several advances that have made surgical treatment safer, less expensive and more effective. These include day-case surgery, stripping to the knee (as opposed to not stripping or stripping to the ankle) and the use of tourniquets. None of the cost data took account of day-case surgery, which has the potential to reduce the costs associated with surgery.

Stripping of the LSV

Five papers[115–119] and two published abstracts[120,121] describe three RCTs comparing stripping of the LSV to the knee with not stripping the vein.. Three papers report separate trials comparing stripping to the ankle with not stripping the LSV.[122–124]

Two trials were identified which considered aspects of stripping technique. Corbett and Harries[125] compared plastic and metal strippers and found no significant difference in outcome in terms of technical operative success. Khan and colleagues[126] carried out a pseudo-randomised trial which compared stripping to the knee with sequential avulsions and found some difference in pain and bruising at 1 week in favour of sequential avulsion, but no longer term differences.

Three papers report separate trials dealing with the direction of stripping the full length of the LSV.[127–129] Seven papers report six trials comparing invagination stripping with standard stripping of the LSV.[130–136] Only one study, by Holme and colleagues,[137,138] was found that compared stripping of the LSV to the knee with stripping to the ankle.

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The overall quality of the studies included in the reviews was variable. Very few studies specifically stated their method of randomisation of patients. This is a major failing and significantly affects the quality of the studies on critical appraisal. The numbers of participants involved in the majority of studies was small and only one study contained a power calculation to estimate sample size.[135,136] Most studies stated their inclusion criteria but the reporting of exclusion criteria was less common and was not always explicit.

The majority of studies described their methods of carrying out the intervention well, although this had been edited in some of the shorter publications. In many cases blinding of patients was described but very few clinicians providing the treatment were blinded, as this was usually unavoidable.

The reporting of the results was again variable and was generally better with studies published more recently. The numbers lost to follow-up were not always described. Few papers stated the methods used to improve their losses to follow-up or reasons for exclusion. An explicit statement of analysis being on an intention-to-treat (ITT) basis tended to be associated with the more recently published studies.

Outcome measures were generally reported well, but in some cases their validity could be questioned. In addition, the outcome measures used were not reproducible or comparable between studies. An example of this could be seen where subjective measures of pain or satisfaction were used. The most common method of assessing these was by visual analogue scale (VAS) or a scoring system. These were created specifically for each study and had not been piloted or validated.

Measurement of complications was open to criticism. Some, such as numbness in the saphenous nerve region, may have existed prior to surgery. Only a minority of the studies stated that they checked for this before hand.

Much controversy exists about the need for stripping the LSV, the level to which it should be stripped, in which direction and with what technique. Fears about stripping include the risk of deep vein damage, increased trauma to the tissues and damage to the saphenous nerve, set against the potential benefit in reducing recurrence rates. The increasing use of coronary artery bypass grafting raises additional issues about the potential advantages of preserving the LSV for use as a bypass conduit.

The studies included in this systematic review were of variable quality, and the reporting of important aspects related to trial quality could have been much improved. Studies that were published more recently tended to be better and this may be related to an increased awareness of quality resulting from initiatives such as the CONSORT statement.[139] An important problem was the diversity of the outcome measures used and this precluded any meta-analysis. The lack of clearly defined outcome measures is a continuing problem in assessing outcomes of varicose vein surgery.

However, there are some conclusions that can be drawn. Stripping the LSV appears to produce a better result, both clinically and functionally. This advantage was seen at 2 years but at 5 years the recurrence rates were similar. Duplex examination suggested that neovascularisation was the most common cause of recurrent saphenofemoral junction (SFJ) reflux, and that this was generally because of new connections between the area of the SFJ and an intact refluxing LSV. In patients who had the LSV stripped the re-operation rate was found to be significantly reduced.

Stripping the LSV to the ankle was not associated with any differences in terms of patients' perception and, more importantly, the incidence of saphenous nerve injuries was significantly increased compared with stripping to the knee level. When the strip was extended to the ankle the direction of the strip seemed to be important in terms of nerve injury, being higher when stripping was done upwards (ankle to groin).

When comparing invagination perforate-invaginate (PIN) stripping and conventional stripping with an olive, there appeared to be no difference between the two techniques. In addition, the technical failure rate of the invagination PIN stripper was a concern. No differences were shown for strippers made of different materials.

When examining stripping versus perforator ligation, thus preserving the LSV for future use as an arterial conduit, three studies showed no significant differences but these trials were not of the highest quality.

There is no randomised trial currently available that considers the cost-effectiveness of stripping the LSV in varicose vein surgery.

Use of tourniquet

Tourniquets have been used as means to exsanguinate limbs when there is a risk of significant blood loss, such as in orthopaedic surgery.[140] However, there are potential problems in using tourniquets on the lower limbs such as thrombosis[141] and nerve damage.[142] The nature of varicose vein surgery is such that the potential for blood loss could be significant and this has led to some authors advocating the use of tourniquets.[143–145]

There are a number of potential tourniquets in widespread use, including the Rhys-Davies cuff[146] and Lofquist cuff.[147] The Rhys-Davies cuff was developed as a means for exsanguination of limbs during orthopaedic operations.[146] The Lofquist cuff,[147] also known by its manufacturer's name the Boazal cuff, is a pneumatic tourniquet originally invented by Dr Johan Löfqvist.

Twenty papers were identified from the search strategy that were potential RCTs evaluating tourniquets in surgery for varicose veins. One was a study identified from the National Research Register,[147] which was subsequently published and included in the review,[145] 10 were non-randomised cohort studies,[144,147–155] two were review articles,[156,157] one was a description of surgical technique,[158] one was a postal questionnaire,[159] one was a duplicate publication[145] and one was a letter commenting on the use of tourniquets.[143]

Three trials were identified dealing with the use of a tourniquet for varicose vein surgery.[145,160,161] These trials randomised 176 patients and 211 limbs to either using a tourniquet during the varicose vein operation or not using a tourniquet. All showed a significant but small (about 100 ml) reduction in blood loss when a tourniquet was used, without reports of significant complications.

The methodological quality of the included studies was relatively poor. The studies had small sample sizes and there were no *a priori* sample size calculations performed for any of the studies. The methods of randomisation were also poorly reported and the blinding to allocation was unclear. One trial, by Corbett and Jayakumar,[160] reported that randomisation was on the basis of toss of a coin by the anaesthetist and another, by Sykes and colleagues,[145] that sealed envelopes were used. However, details were missing on how the randomisation sequence was generated. The final trial, by Thompson and colleagues,[161] simply reported in the abstract that it was a randomised study and provided no other details.

All the trials examined the effect of using a tourniquet in terms of total blood loss. However, there were variations in defining total blood loss and how it was measured, with only Corbett and Jayakumar[160] reporting how the blood loss was estimated. This lack of detail in the other two trials could mean that there were significant variations in how total blood loss was estimated. Furthermore, Corbett and Jayakumar[160] and Thompson and colleagues[161] reported mean blood loss and Sykes and colleagues[145] reported median blood loss.

All the trials included operative time as an outcome measure, but there were variations in how this was measured. Corbett and Jayakumar[160] defined the operative time from the start of the avulsions until the start of dressing the wounds. However, Thompson and colleagues[161] defined it as the time from entering theatre to completion of the dressings. No details were provided in the other trial. None of the trials determined the relative cost-effectiveness of the use of a tourniquet.

The available evidence on the evaluation of the use of tourniquets in varicose vein operations is limited to three RCTs. These trials were all of poor quality and had deficiencies in trial design, sample size and measurement of outcomes. None of the trials had sufficient power and sample size to determine the differences between use or non-use of a tourniquet during varicose vein surgery. Also, they were not of sufficient size to determine the incidence of potential relatively rare complications such as nerve damage or arterial injury (especially in older patients). This is a consideration when recommending the use of tourniquets. As large numbers of varicose vein operations are undertaken, there is the potential for a significant number of additional complications not reported in these trials to be caused by using a tourniquet. There were also variations in how outcomes were measured, with two trials reporting means and the other medians.

Despite these limitations, all three trials agreed that the amount of blood loss can be significantly reduced when using a tourniquet with no significant increase in operating time, reported adverse events or subjective outcome. The mean and median total blood loss was relatively small in both groups and not necessarily clinically significant. However, without a tourniquet there was a wider range of total blood loss and those in the upper limits potentially lost enough blood to require a blood transfusion. A further

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consideration is that any potential for reduction of exposure to blood for healthcare staff should be considered in the light of the possibilities of blood-borne diseases such as HIV and hepatitis C.

A reduction in blood loss could result in a reduction of post-operative bruising, but this was included as an outcome measure in only one trial, by Sykes and colleagues.[145] Although it reported a significant reduction in the area of bruising with the use of a tourniquet, the trial had a relatively small sample size of 25 patients in each arm.

None of the trials explored the cost-effectiveness of the use or non-use of a tourniquet. The trials did not find any increase in the largest potential cost, which was length of operation. Also, there were no discussions of the costs of the tourniquets, other equipment or any additional potential costs such as staffing or training.

Sclerotherapy versus conservative treatment

High-quality evidence was already available regarding sclerotherapy versus conservative treatments in the form of a Cochrane Collaboration systematic review undertaken by Tisi and Beverley.[103]

Their review aimed to examine all RCTs comparing injection sclerotherapy and conservative treatments (graduated compression stockings and/or observation). They also examined differences in sclerosants and techniques for sclerotherapy. However, they included sclerotherapy for thread veins in addition to varicose veins.

The search strategy and methods for the review followed standard Cochrane Collaboration methodology and can be found in their review article. The methods were comparable to those used in reviews undertaken by ourselves.

A total of 28 studies were identified for inclusion in their review. Of these, 16 were excluded as they did not meet the inclusion criteria or were non-randomised studies. The remaining 12 studies were included in the review. These studies examined six different aspects:

1. sclerotherapy with sodium tetradecyl sulphate (STD) versus alternate sclerosants
2. local anaesthetic (LA) versus no LA
3. use of Moleform versus Sorbo pads at injection sites after sclerotherapy
4. use of elastic compression versus conventional bandaging after sclerotherapy
5. short-term versus standard bandaging after sclerotherapy
6. sclerotherapy versus graduated compression stockings.

The last comparison was of most interest in terms of the evidence for different treatments of varicose veins.

No RCTs were found that compared sclerotherapy with simple observation. One trial was found that compared sclerotherapy with graduated stockings.[162] The trial was conducted in 1973 and showed advantage in terms of symptoms and cosmetic appearance for sclerotherapy [relative risk (RR) 1.61, 95% CI 1.19 to 2.18].

The review concluded that there was no evidence to support the claims of Fegan[56] regarding the type and duration of compression following sclerotherapy. Tissi and Beverley found no differences between various types and duration of compression on the incidence of superficial thrombophlebitis, obliteration of varicose veins or recurrence rate. In addition, they found no difference between the strength of STD used.

Tisi and Beverley[103] showed in their review that the available evidence on the effectiveness of sclerotherapy in the treatment of varicose veins was limited and of poor quality. There was a particular lack of evidence comparing sclerotherapy with compression stockings, with only one trial found that examined pregnant women.

Other treatments

Eighteen potential studies were identified evaluating the effectiveness of other treatments for varicose veins. However, five were non-randomised studies and five evaluated compression and chronic venous insufficiency with or without the presence of varicose veins. Six studies described in eight papers were included. No trials were identified that compared surgery with observation or sclerotherapy with observation.

Hence six trials were identified that examined other non-surgical interventions for varicose veins.[163–168] Four of these examined drugs.[163–165,168] one a homeopathic preparation[166] and one hydrotherapy.[167,169,170]

Two of the drug studies[165,168] assessed oxerutins (a group of chemicals derived from a naturally occurring bioflavonoid called rutin). Both studies found no statistically significant differences between those randomised to oxerutins and those randomised to placebo.

The other two drug studies randomised between heptaminol adenosine phosphate (a cardiac stimulant and vasodilator) and placebo[163] and between calcium dobesilate (a vasoprotectant and capillary dilator) and placebo.[164] Schmidt and colleagues[163] showed significant improvement in venous outflow measured by plethysmography but did not measure any clinical outcomes. Androulakis[164] also reported significant improvements for patients on the drug treatment, measured by plethysmography, which correlated with subjective improvements. However, there were a significant number of withdrawals and the analysis was not ITT.

Ernst and colleagues[166] randomised patients between a homeopathic preparation (Poikiven) and placebo. They reported significant improvements in objective measures (plethysmography and leg circumference) but there were significant differences between the groups at baseline and the analysis was not ITT.

The final trial[167,169,170] randomised between hydrotherapy and no hydrotherapy. The study reported significant reductions in leg volumes and ankle/calf circumference for the hydrotherapy group.

No clear evidence has been found that alternative therapies offer a more beneficial form of treatment in terms of symptom relief. None of these treatments removed the cosmetic element of varicose veins, a factor that is often important to patients and a driving force behind them seeking treatment. The evidence presented about the drug therapies concerns small numbers of patients and raises doubts about drug tolerability and efficacy. Many of the changes in the objective symptoms are only small and it is unclear how these can be interpreted in terms of clinical improvement. There are no trials which duplicate the interventions and therefore can substantiate or disagree with their findings. Conventional treatments have been the subject of multiple clinical trials and the evidence currently appears to be that the alternative therapies cannot offer a convincing replacement for the conventional therapies.

There is no evidence regarding costs for these treatments as they are purely experimental drugs at the moment and are not routinely being used anywhere. No costs for hydrotherapy were reported.

Key points

- Published studies of varicose vein treatments are hampered by the lack of a widely accepted classification of the extent of varicose veins and consistent definitions of recurrence.
- Trials comparing surgery with sclerotherapy suggest that the outcomes of sclerotherapy deteriorate over the first few years and all trials with follow-up of ≥ 3 years are consistent in showing benefit for surgical treatment.
- Evidence regarding stripping of the LSV suggests that this technique reduces recurrence rates, at least in the early years. There is no evidence to suggest a benefit for stripping to the ankle and this produces a greater rate of saphenous nerve injury, especially when the direction of stripping is from ankle to groin. No benefit was found for alternative stripper devices or for invagination stripping.
- The use of a surgical tourniquet during surgery results in lower operative blood loss without any reported increase in complications.
- Evidence for the effectiveness of sclerotherapy and for benefits of individual techniques or sclerosants was inadequate to draw firm conclusions.
- There is inadequate evidence to support the use of drug or alternative therapies in the management of varicose veins.

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Chapter 3

Classification of varicose veins

Background

As described above, previous research relating to varicose veins has suffered from a lack of a generally agreed and workable classification system to stratify recruited patients and judge the extent of the condition and outcomes of treatment. One of the initial tasks for the trial participants was to identify an anatomical classification of varicose veins that could be applied consistently by trial participants, would provide a system of classification with a direct and pragmatic bearing on treatment and was applicable to a clinical setting.

To this end, a project was set up to develop a pragmatic classification of uncomplicated varicose veins using a modified nominal group process approach.[171]

Methods

Development was through an iterative process in which a group of interested participants within the trial met to reach consensus on the content and form of the classification. The process went though a number of stages:

- The group met and agreed a set of criteria that should be fulfilled by an ideal classification.
- A literature search was carried out to identify existing systems of classification for varicose veins and copies of appropriate papers were obtained and circulated to participants in the group.
- The group met and considered existing classifications against the proposed criteria.
- Group members put forward suggestions and a consensus was reached regarding a provisional classification.
- A pilot study was carried out in which new referrals with varicose veins were independently examined and classified by members of the group.
- The results of this study were summarised to the trial participants with a list of the items that caused discrepancy in the classification and a consensus was reached about necessary amendments.

Results

The criteria agreed by the group are listed in *Table 5*.

Literature review

The literature review identified 10 classification systems based on anatomical features of varicose veins. Of these, there were two that had been widely used in other studies.

The Basle system[85,172] was felt to be unsatisfactory for a number of reasons:

- The grading system was based on 'degree and extent of tortuousity and prominence', which was not thought to be open to objective evaluation.
- The system used a variety of terms that were unfamiliar to most current clinical staff.
- It made no reference to any use of Doppler examination or assessment of reflux.
- It was felt that the system could not be widely applied without special expertise.
- There were no clear links with options for clinical management.

TABLE 5 *Characteristics of proposed criteria for the classification of varicose veins*

• The process should be simple, easily understood and learnt by staff at all levels
• It should be suitable for use in an outpatient clinic without special equipment or additional resource requirements
• There should be an acceptable level of inter- or intra-observer variation
• It could take into account frequently used methods of assessment, including inspection, physical and HHD examination, but should not require the results of additional special investigations
• It should have a direct and pragmatic bearing on treatment. Hence factors which have a significant impact on the suitability for surgery or sclerotherapy should be taken into consideration
• It should be easily applicable to both scientific studies and routine clinical practice
• Varicose veins should be distinguished from thread veins

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The CEAP classification[173] is a comprehensive system, which attempts to describe the whole spectrum of venous problems. The anatomical part of the classification does not take into account the size or extent of varicosities and it was felt that the system was complex and difficult to learn.

Of the other classifications reviewed, all were felt to be unsatisfactory as they required special investigations,[174–177] related specifically to recurrent varicose veins[178] or provided no measures of the extent of varicosities or of a distinction between those AK or BK.[89,179]

Proposed classification system

A consensus was reached on the following items that were felt to be relevant to the classification.

- Distinction between thread veins and varicose veins, the former being excluded from the classification.
- Site (upper thigh, lower thigh, BK), size and extent of varicose veins as these have a bearing on the suitability for sclerotherapy and duration of surgery.
- The presence of groin, LSV or popliteal fossa reflux based on an HHD examination.
- Medical complications, including ulceration and skin changes.
- Recurrent varicose veins in which a redo saphenofemoral or saphenopopliteal ligation would be required.

Pilot study

Eleven patients referred to a vascular outpatient clinic with a diagnosis of varicose veins were examined by between three and seven members of staff (four consultant vascular surgeons, a clinical assistant and two vascular surgical trainees). Each patient was assessed independently by several participants using a prepared proforma and grouped according to the worst leg.

TABLE 6 *Criteria for allocation of patients to varicose vein categories*

Definitions

Varicose veins (VVs). Tortuous veins that bulge or protrude. Venous flares, telangiectasia and veins that are easily visible, but do not protrude, are classified as **thread veins**

Quadrant. Extent of varicose veins below the knee is determined by the number of quadrants in which varicose veins are seen. A single quadrant is any contiguous area which covers less than half the circumference of the lower leg over less than half the distance from knee to malleolus

Size. Varicose veins greater or less than 5 mm as determined by the maximum diameter of any varicose vein with the patient standing

Significant skin changes. Lipodermatosclerosis, eczema or skin pigmentation (but excluding small areas of light pigmentation)

Reflux. As determined by HHD examination in the groin, in the LSV just above the knee and on examination of the popliteal fossa. The time threshold for significant reflux is 1 s, but examiners may use their discretion in excluding reflux of >1 s, which sounds soft and unimportant or, for example, is present in a small superficial varicose vein crossing the popliteal fossa

The worst leg[a]. This is the leg which the patient considers to be more symptomatic

Definition of groups

Thread veins only – As defined above

Group 1 – No significant reflux in the groin/LSV or popliteal fossa. Varicose veins restricted to below the knee or <5 mm in diameter in the lower two-thirds of the thigh

Group 2 – Reflux >1 s at groin, LSV or popliteal fossa. Varicose veins <5 mm in the lower two-thirds of thigh and/or below the knee (any extent below knee varicose veins but must not be >5 mm in more than one quadrant)

Group 3 – Any patient with significant skin changes, reflux >1 s in the groin, LVS or popliteal fossa. Above-knee varicose veins >5 mm in diameter of any varicose veins in upper third of thigh. Below-knee varicose veins >5 mm in more than one quadrant

Recurrent varicose veins – Patients with demonstrable reflux in the groin or LSV who have undergone previous saphenofemoral ligation, or with popliteal fossa reflux who have undergone previous saphenopopliteal ligation

[a] In clinical practice, a separate grading can be given for each leg. However, for the purposes of trials where the unit of randomisation is likely to be an individual patient, it may be necessary to identify the side that is to be used as a basis for any stratification.

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In six cases, there was complete agreement amongst all assessors on the grading of the varicose veins. In a further two cases, all agreed on the grading based on the proforma, but one observer had incorrectly assigned the grade. In another, one observer incorrectly assigned the patient owing to failure to identify AK varicosities that were observed by four others. In one patient, there were discrepancies due to disagreement as to whether there were thread veins only or minor varicose veins.

In the final patient, some ambiguities in the classification system were identified. First, the more symptomatic leg was less severely affected in anatomical terms and there was uncertainty as to the leg to which the classification applied. Second, there was ambiguity in the classification as to whether a leg with two quadrants affected, but with large veins in only one, should be allocated to Group 2 or 3.

Based on these discrepancies, some minor modifications were made to the classification system. The final classification is given in *Table 6*.

For the purpose of comparisons within the trial, a single score was derived from the classification as described in *Table 7*. This produced an arbitrary 10-point score (0–9) on which 0 represents the absence of varicose veins in that limb and 9 is the maximum extent, with varicose veins being present in the upper thigh, the lower thigh and all four quadrants BK, with veins of over 5 mm both AK and BK. Further details of the classification and pilot study have been previously published.[220]

TABLE 7 *Anatomical score derived from classification of varicose veins (the extent is calculated by summing the scores in the table, giving a range of possible scores from 0 to 9)*

Site	Extent	Score
Upper third of thigh	Absent	0
	Present	1
Lower two-thirds of thigh	Absent	0
	<5 mm	1
	>5 mm	2
Below knee		
Size	Absent	0
	<5 mm	1
	>5 mm	2
Location	Absent	0
	1 quadrant	1
	2 quadrants	2
	3 quadrants	3
	4 quadrants	4

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Chapter 4
Clinical trials

Methods

Setting
The study was multicentre and took place in Sheffield and Exeter. The Sheffield site was based on a vascular unit – Sheffield Vascular Institute (SVI) – with five consultant vascular surgeons. The SVI provides a service for two teaching hospital NHS Trusts, the Northern General Hospital NHS Trust and Central Sheffield University Hospital NHS Trust (these merged into the Sheffield Teaching Hospital NHS Trust during the lifetime of the project). The Exeter site was the Royal Devon and Exeter Hospital, which is a district general hospital, with a vascular unit of three consultant surgeons.

Objectives
The overall aim of the study was to assess the clinical effectiveness and cost-effectiveness of conservative treatment, compression sclerotherapy and surgery in the management of varicose veins. The stratification of patients based on historical, symptomatic, investigative and demographic features aimed at determining the expected costs and benefits of treatment for mild, moderate and severe varicose veins. This was intended to allow purchasers and providers to set treatment policies for these subgroups of patients and to determine the relative priorities for allocation of resources.

Participants
Ethical approval for the study was obtained from both Sheffield and Exeter Local Research Ethics Committees.

The aim was to recruit all patients referred to the participating centres via their GP with a diagnosis of varicose veins. Recruitment for the project took place between January 1999 and January 2001 (initially a 1-year recruitment period had been planned, but this was extended to 2 years). Patients with recurrent varicose veins were included, after assessment, in the observation arm unless they would have required repeat saphenofemoral or saphenopopliteal ligation.

Design
The study was a prospective clinical and cost-effectiveness study that included three RCTs and an observational group. All patients referred to the two centres underwent a full baseline assessment. They were categorised according to the severity of their symptoms and clinical findings into one of three groups and asked to consent to participate in one of the RCTs. *Table 8* shows the interventions for the RCTs and exclusion criteria for each trial. Patients who refused to consent or who did not meet the inclusion criteria for the RCTs were asked to participate in the observational group. A flow chart was developed to aid in the allocation of patients to the appropriate group (*Figure 2*).

Sample size
At the start of the study, it was estimated that an RCT of 200 patients (100 in each group) would provide a sufficient number to detect a 0.075 change in utility health scores (5% significance, 80% power). Based on the number of referrals in the few years prior to commencement of the study, it was estimated that there would be about 500 new referrals per year at each centre. Assuming an exclusion rate of 20% and allowing for an uneven split between the proposed trials, it was expected that recruitment of 1000 patients would be required to produce this sample size in each arm of the study, and would take approximately 1 year to achieve.

Informed consent
Patients were given an information leaflet describing the trial prior to their attendance for assessment at the vascular outpatients. A research nurse discussed the project with the patient and the patient was given an opportunity to ask questions and raise any concerns regarding the project. They were then invited to participate in the study. Participants were made aware that they could withdraw from the trial at any time, without giving a reason and without it affecting their current or future care. Examples of the information sheets that were used in the study are provided in Appendix 2.

Randomisation procedure
After informed consent had been obtained and the arm of the trial appropriate to each patient had been determined, patients were randomised to one of the two interventions in that arm of the

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TABLE 8 *Exclusion criteria and allocated interventions for participants in observational and randomised controlled trials*

General exclusion criteria		
• Unwillingness to give informed consent • Unwilling or unable to complete assessment protocol • Current evidence of thrombophlebitis, ulceration or DVT		
		Specific exclusion criteria
Group 1	Sclerotherapy vs conservative treatment	• Patients with deep venous insufficiency confirmed by duplex • Allergy to sclerosant • Diameter of varicose veins >2 cm
Group 2	Sclerotherapy vs surgery	• Patients with deep venous insufficiency confirmed by duplex • Allergy to sclerosant • Diameter of varicose veins >2 cm • Pre-existing co-morbidities that would make them unsuitable for surgery • BMI >32
Group 3	Surgery vs conservative treatment	• Patients with deep venous insufficiency confirmed by duplex • Allergy to sclerosant • Diameter of varicose veins >2 cm • Pre-existing co-morbidities that would make them unsuitable for surgery. • BMI >32

trial (see *Table 9*). Randomisation was based on the individual participant and where bilateral veins were present the unit of randomisation was the 'worst' leg based on the patient's decision on which was their worst leg. Random treatment allocation was based on a computer-generated random number list and a telephone randomisation service. A trial identification number and intervention were allocated to the patient.

Blinding

It was not possible to blind the patient or researchers to the treatment allocation. However, the surgeon performing the HHD assessment and the vascular technologist performing the duplex scan were blinded to each other's findings.

Interventions

Group 1. Sclerotherapy versus conservative treatment

This group comprised patients with minor BK varicose veins whose main symptoms were related to cosmetic appearance and aching and who did not have any evidence of reflux or complications. Participants were randomised between sclerotherapy and conservative treatment.

Sclerotherapy protocol

Sclerotherapy was performed as an outpatient procedure. Exeter had a long-established dedicated sclerotherapy clinic, whereas in Sheffield a clinic was established for the purposes of the trial. Varicosities were injected with 3% STD, then compression was applied using foam pads and a class II graduated compression stocking or bandage was applied all the way up the leg from the foot. Patients were asked to re-attend outpatients 2 weeks later to check whether their sclerotherapy treatment had been successful and further injections were performed if necessary.

Conservative treatment

Conservative treatment consisted of advice to the patient regarding lifestyle, in particular:

- the importance of regular exercise and leg elevation to help relieve the symptoms of varicose veins
- eating and maintaining a healthy diet to reach their ideal body weight
- wearing class I, II or III support stockings or tights that are well fitted and comfortable to counteract the high pressure in the veins and to give relief from their symptoms
- advice on the impact of work and pregnancy on symptoms

Group 2. Sclerotherapy versus surgical treatment

This group comprised patients with moderate below knee varicose veins associated with saphenofemoral or saphenopopliteal reflux.

Sclerotherapy was performed as described for Group 1.

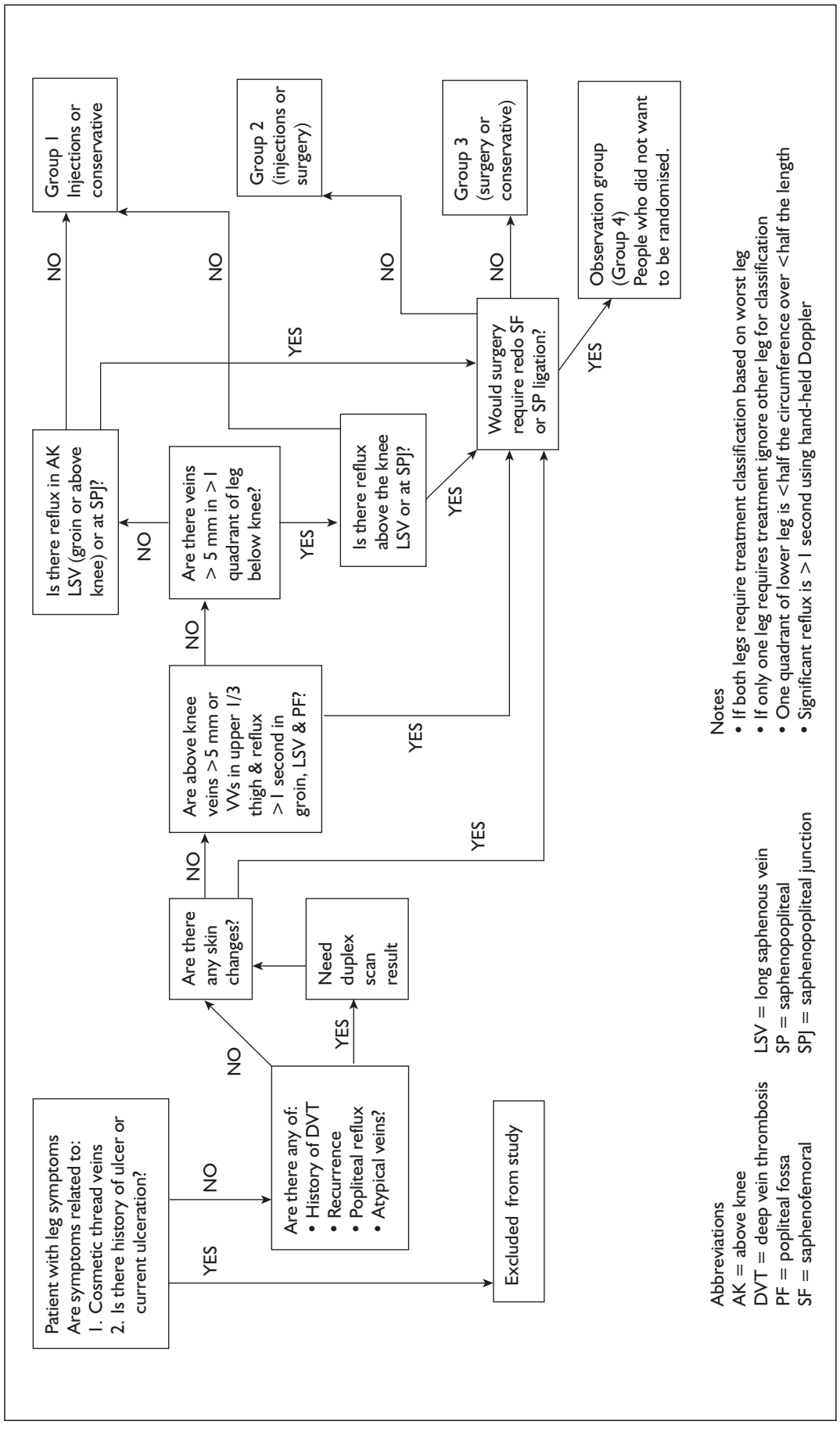

FIGURE 2 *Treatment allocation algorithm*

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TABLE 9 *Baseline assessment procedure used for all potential trial participants*

1. **Prior to outpatient appointment** – Participants were provided with information about the study and asked to complete a questionnaire (see Appendix 3A). This included questions about demographic data, smoking and the use of compression hosiery
2. **Initial interview** – The project was explained to the patients and informed consent was obtained before any assessment
3. **Assessments by medical staff –**
   - The research nurse completed a baseline proforma which noted the patient's demographic data, past medical history and the symptoms related to their varicose veins (see Appendix 3A)
   - A member of medical staff completed a full clinical examination. This included assessment of anatomical distribution, number of quadrants and extent of varicose veins and an HHD assessment (see Appendix 3B). The patient was allocated to an treatment group based upon the classification in Chapter 3 (see *Figure 1*).
4. **Patient questionnaire** – The patient brought this to outpatients. The questionnaire contained the SF-36 and EQ-5D quality of life assessments
5. **Standard gamble** – A standard gamble question related to patients' assessment of their current health state was administered by the research nurse. Standard gamble is based on the respondent making a choice between their current health state (the certain outcome) and full health (the uncertain outcome). The probability of full health was varied until the respondent was indifferent between the certain and uncertain outcomes
6. **Colour duplex assessment** – This was undertaken in the vascular laboratory by vascular technologists, blind to the findings of the clinical and HHD examination. Some of these were carried out on the day of the outpatient clinic visit and others required the patient to return on a separate occasion

Surgical treatment protocol
Uncomplicated unilateral varicose vein operations were performed on a day-case basis. Patients with more complex varicose veins were admitted for an overnight stay at the discretion of the surgeon. Surgery was carried out by a consultant or specialist registrar with appropriate experience. For patients requiring long saphenous surgery, flush ligation of the vein was done at the saphenofemoral junction, with division of all second-order tributaries within 2 cm of the junction, through a groin skin crease incision. The LSV was stripped to a level just above or below the knee. For patients requiring short saphenous surgery, ligation of the vein was done as close as possible to the saphenopopliteal junction through a transverse incision, sited according to Doppler marking.

Phlebectomies were performed, through small vertical stab incisions. Most surgeons in Sheffield exsanguinated the limb with a tourniquet before performing phlebectomies. Groin (and popliteal fossa) wounds were closed with absorbable dermal sutures after infiltration of LA. Phlebectomy wounds were closed with adhesive strips.

Compression was applied to the limb at the end of the operation and left in place for a number of days thereafter. This was done differently in Sheffield and in Exeter, as follows. In Sheffield, two Panelast bandages were applied to the leg in a spiral with half width overlap. These bandages were left in place for 7–10 days, and TED anti-embolism stockings [Kendall Co (UK) Ltd] were then applied by a community nurse and worn for 7–10 days. In Exeter, two cotton-wool bandages (Velband by Johnson & Johnson Ltd) were applied to the limb, followed by two or three 15-cm diameter crepe bandages, applied firmly with at least half width overlap. These were changed the following day for a thigh-length TED antiembolism stocking, which patients were advised to wear for 10 days.

Group 3. Surgery versus conservative treatment
This group consisted of patients with extensive varicose veins that were AK and also BK with signs of reflux in the saphenofemoral or saphenopopliteal veins. Surgical treatment was as in Group 2.

Observation group
The observation group consisted of those patients who either refused randomisation, as they had a preference for a particular treatment, and those who were excluded from one or both of the treatment options available for their allocated group. Treatment was on the basis of patient choice in consultation with medical staff. Those who chose surgery or sclerotherapy followed the same treatment protocols as those included in the randomised group. Patients unsuitable for sclerotherapy or surgery were treated conservatively.

Outcomes
The primary outcome measure for the study was clinical effectiveness, as measured using the Short Form 6D (SF-6D) utility valuation. The study also included a cost-effectiveness analysis (described in Chapter 5). Secondary outcomes included

complications of treatment, symptomatic relief, HRQoL and patient satisfaction. HRQoL was measured using the Short Form with 36 Items (SF-36), EuroQol quality of life questionnaire (EQ-5D) and standard gamble questionnaires.

The changes in utility scores were estimated using the algorithm for the SF-36 as described by Brazier and colleagues.[180]

The EQ-5D is a non-disease-specific means of describing and valuing HRQoL.[181,182] The first part of the EQ-5D asks respondents to categorise their current health status on five dimensions (mobility, self-care, usual activities, pain and anxiety/depression), where each dimension has three possible levels of response. In the second part of the instrument, respondents are asked to value their current health status using a vertical rating scale presented like a thermometer, which is labelled with 'best imaginable health state' at the top and 'worst imaginable health state' at the bottom. The EQ-5D results are presented using the tariff of mean values for health states produced by the Measurement and Valuation of Health (MVH) group based upon the time trade-off (TTO) scaling technique.[183] In addition, for comparative purposes, the EuroQol VAS scores are also presented, which reflect the patient's valuations of their own health state on the vertical rating scale.

Economic analysis

Details of the methods for the economic analysis and an additional WTP exercise are described in Chapter 5.

Costings

All relevant resource use by the patients in the three trials was recorded. The costings concentrated on the differences in resource use between the treatment options in each of the three trials in line with established economic methods. Data were collected on:

- the length of time patients spent in hospital: the duration of the treatment procedure
- staff grades and time spent at each stage of the patients' hospital stay
- consumables and equipment used
- overheads.

Capital was amortised at the recommended Treasury rate of 3.5%.[184]

Patient notes and hospital records were the primary data sources and estimates were made of patients' use of hospital and other healthcare services through questionnaires administered during the trial.

Assessment and follow-up

Initial assessment included self-completed questionnaires, interview with research nurse, medical examination, standard gamble interview and colour duplex assessment. Details of the assessment protocol are shown in *Table 9* and Appendix 3 provides examples of the patient information, questionnaires and data collection forms.

Postal HRQoL questionnaires were sent to the patients in both the randomised and observation groups 1 and 6 months after treatment. Those who did not respond were contacted by telephone asking them to do so. One year after treatment patients were seen in the outpatient clinic for a full assessment of their symptoms and the distribution and extent of any varicose veins. Patients completed a questionnaire that included the SF-36 and EQ-5D, and that also asked about symptoms and about contacts with healthcare services and professionals since the time of treatment (see Appendices 3D and 3E). Postal questionnaires were sent to all randomised patients 2 and 3 years after treatment. The follow-up protocol is shown in *Table 10*.

Analysis of data

Details of the economic analysis and modelling are given in Chapters 5 and 6.

Analysis of outcomes was on an ITT basis. Data from the assessments and questionnaires were coded and analysed using SPSS, Excel and DATA (a specialist decision modelling software package, TreeAge Inc.). Differences in means of continuous variables were estimated using *t*-test and analysis of variance (ANOVA) and differences in proportions using a χ^2 test. Categorical data were compared using Fisher's exact test, χ^2 test or χ^2 test for trend, as appropriate.

Results

Introduction

As described above, patients were allocated to specific arms of the clinical trial, on the basis of the initial clinical assessment. Group 1 patients were offered randomisation between conservative treatment and sclerotherapy, Group 2 patients between sclerotherapy and surgery and Group 3 patients randomisation between conservative

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TABLE 10 *Follow-up protocol*

Patient allocated treatment	Date of treatment recorded – conservative, sclerotherapy or surgery
1 month after any treatment	SF-36 questionnaire and EQ-5D were sent to all patients
6 months after treatment	SF-36 questionnaire and EQ-5D were sent to all patients
1 year after treatment	An outpatient appointment was arranged with a research nurse for assessment and clinical examination. Advice was given about conservative measures. A proforma, SF-36 questionnaire and EQ-5D and standard gamble technique were used (see Appendix 3)
2-year questionnaire (only those patients randomised)	An SF-36 questionnaire and EQ-5D were sent to all randomised patients
3-year questionnaire (only those patients randomised)	An SF-36 questionnaire and EQ-5D were sent to all randomised patients

treatment and surgery. Those patients who declined randomisation in any of these arms, along with those who had exclusions to the clinical trial, formed the observational arm of the study. For the purposes of the presentation of the results, details of the overall patient population will be described along with the distribution to the various clinical trial groups. Each of the randomised groups will then be presented and the results analysed on an ITT basis. Following this the results of the observational data on the entire cohort will be presented with results based upon actual treatments undertaken.

Patient population

Recruitment

Over the period from 1 January 1999 to 7 January 2001, all referral letters at both participating centres were screened for a diagnosis of varicose veins. All patients with such a diagnosis on the referral letter were booked into designated outpatient clinics. Over the full period, 1841 clinic bookings were made and 249 (14%) cancelled or failed to attend appointments, some of whom re-booked on another occasion.

A total of 1592 patients were seen in clinics and a further 214 (13%) were excluded as they had purely cosmetic thread veins or had some other reason for their referral, with varicose veins not being the main presenting complaint. This left 1378 patients who were theoretically available for recruitment, of whom 289 declined participation and a further 89 were lost to the trial for other reasons (e.g. seen in clinics without research staff available or not sent preliminary information regarding the trial). No further information is available on those who declined participation at this stage. There remained 1009 patients who were recruited to the trial (*Figure 3*).

During the first year of the trial, the recruitment, particularly to the randomised arms of the trials, was slower than had initially been predicted. For this reason, the initial recruitment period was extended to a second year. At this time there was a change in practice, in that owing to limited research clinic capacity and the desire to maximise recruitment to the randomised arms of the trials, some patients who would clearly not be eligible for randomisation on the basis of the contents of their referral letter were booked into non-research clinics. These patients were therefore not available to the observational arm of the trial.

Of the 1009 patients recruited, 226 (22%) were excluded from randomisation. The main reasons for exclusion were a body mass index (BMI) of >30, recurrent disease, skin changes and lack of fitness for surgery due to coexisting disease. Several patients had more than one reason for exclusion (*Table 11*). Of the 783 patients who were suitable for randomisation, 64 (8%) were classified as Group 1, 183 (23%) Group 2 and 563 (72%) Group 3 based on the classification system described in Chapter 3. Overall 357 patients (46%) agreed to be randomised, with the highest proportion of eligible patients (53%) being in Group 1. The details of the number of patients randomised in each group and a flow chart showing the numbers randomised to the various treatment options in each arm of the trial are shown in *Figure 4*. Those patients who were prepared to participate in the trial but declined randomisation were followed up with the same protocol as those having mandatory observation and together these constituted the observational arm of the trial (Group 4), consisting of 652 patients.

Protocol violations

A total of 75 patients (7.4%) appear to have been allocated to the incorrect group on the basis of the

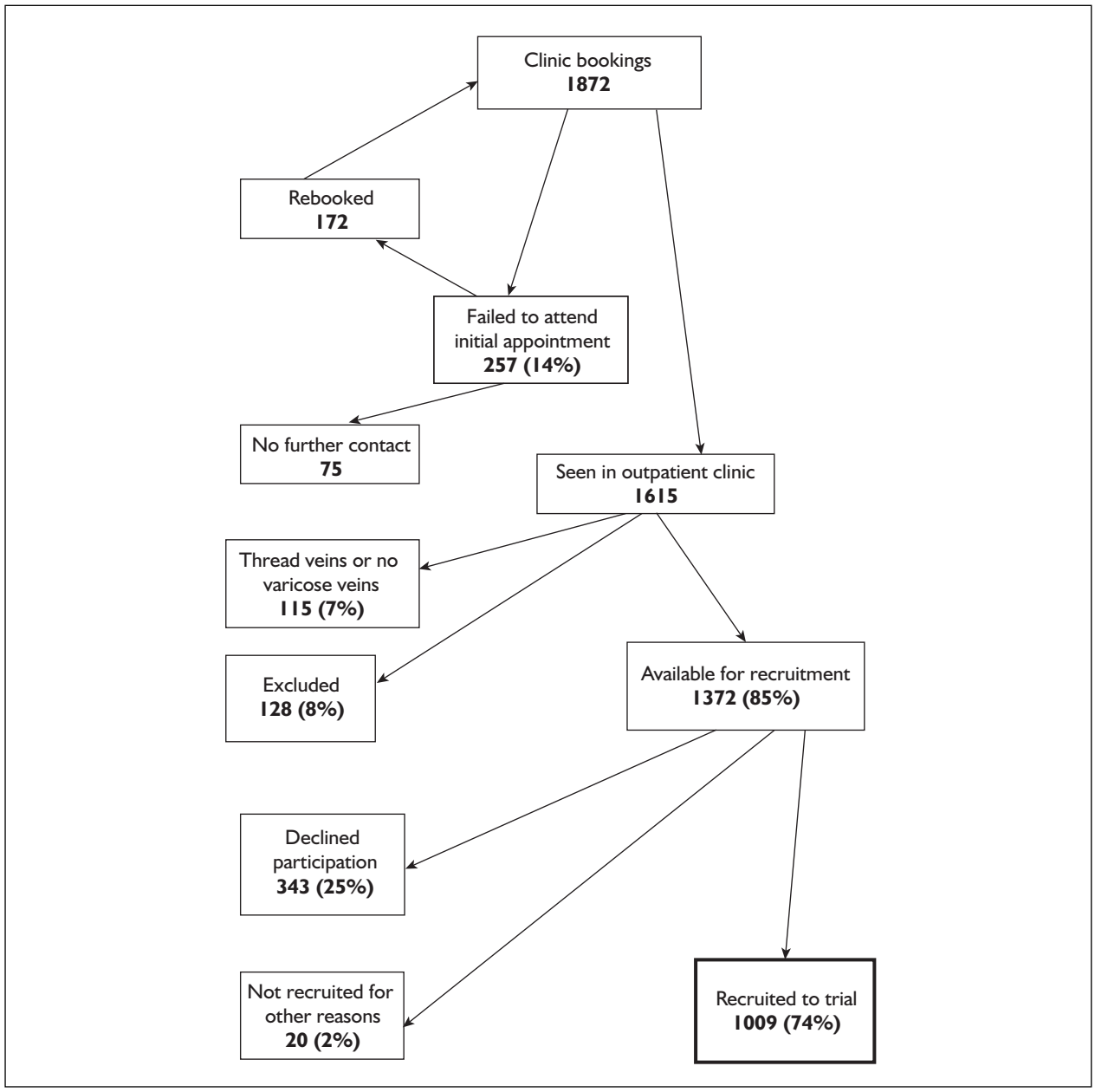

FIGURE 3 *Recruitment of patients to trial from consecutive referral letters suggesting a diagnosis of varicose veins*

TABLE 11 *Reasons for mandatory exclusion from randomisation (subjects may have more than one reason listed)*

Reasons for exclusion	No. of patients	Percentage
BMI >30	110	48.7
Skin changes	74	32.7
Recurrence	72	31.9
Past history of DVT or fracture	30	13.3
Co-existing disease		
Respiratory	33	14.6
Cardiac	13	5.8
Arterial disease in leg	8	3.5
No. of excluded patients	**226**	

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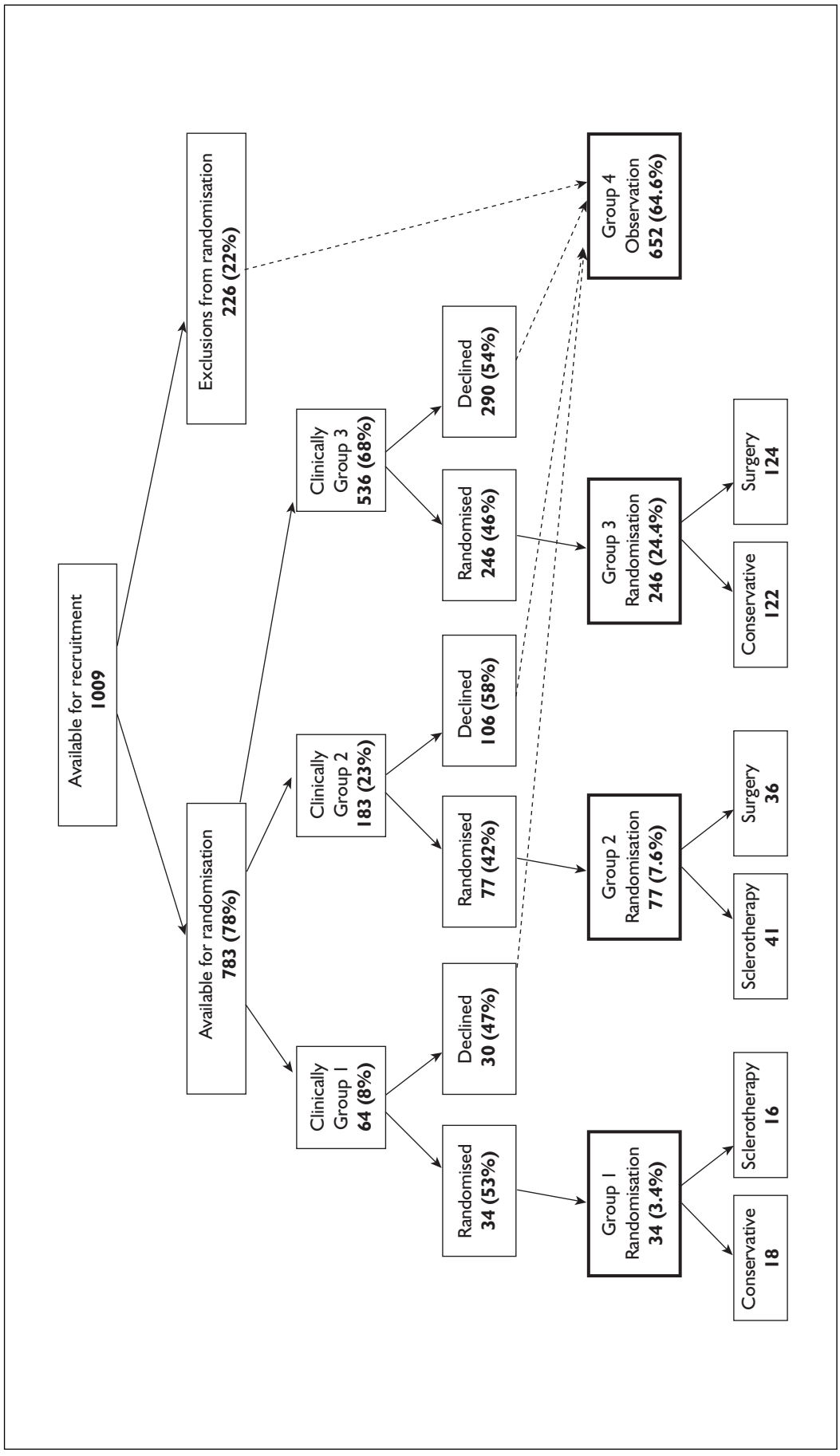

FIGURE 4 *Recruitment to RCTs*

TABLE 12 *Breaches of protocol*

Randomised with BMI >30	42
Patients with upper thigh varicosities allocated to Group 1 or 2	11
Patients with lower thigh varicosities of >5 mm allocated to Group 1 or 2	6
Patients with reflux identified allocated to Group 1	3
Patients who would appear in Group 1 or 2 on anatomical extent allocated to Group 3	20
Total patients (some having more than one breach of protocol)	**75 (7.4%)**

TABLE 13 *Demographics and clinical features of referrals by intended treatment group*

	1	2	3	Mandatory observation	Total
N	64	183	536	226	1009
Sheffield:Exeter	31:33	86:97	244:292	107:119	468:541
Female:male	54:10[a]	147:36[a]	359:177[a]	167:59[a]	727:282
Age (SD) (years)	46.5 (12.7)	46.7 (13.7)	50.4 (13.5)	52.7 (12.9)	50.0 (13.5)
Height (SD) (cm)	165.7 (8.0)	166.8 (8.7)	168.4 (10.1)	166.6 (9.5)	167.6 (9.6)
BMI (SD)	24.9 (4.3)	25.6 (3.5)	25.9 (3.5)	30.7 (6.0)	26.8 (4.6)
Smokers	16 (25.0%)	42 (23.0%)	120 (22.4%)	42 (18.6%)	220 (21.8%)
Family history of varicose veins	45 (70.3%)	127 (69.4%)	383 (71.5%)	163 (72.1%)	718 (71.2%)
Family history of leg ulceration	11 (17.2%)	27 (14.8%)	79 (14.7%)	40 (17.7%)	157 (15.6%)
Previous pregnancies (mean no.)	46 (2.1)	124 (1.8)	321 (1.9)	148 (2.3)	639 (2.0)

[a] $p < 0.05$, χ^2 test for trend.

clinical information available on the assessment form. A summary of the protocol violations is shown in *Table 12*. The most common issue was that 42 patients (4.2%) with a BMI of >30 were allocated to randomised limbs of the trial. Most of these had a BMI only slightly above 30 with several having comments that they were in the process of losing weight. Other violations of protocol included the allocation of patients to Group 1 or 2 despite thigh varicosities that should have made them ineligible, although again there were anecdotal comments in some of the assessment forms suggesting that the thigh varicosities were not considered to be clinically relevant. Twenty patients allocated to Group 3 appeared, on the basis of the assessment data, to have veins that would have been suitable for sclerotherapy. However, this may represent a failure of the assessment form to capture adequately issues that the clinicians concerned felt were contraindications to sclerotherapy.

For the purpose of the results of the randomised arms of the trial, all patients were analysed on an ITT basis, irrespective of protocol violations.

Patient demographics and clinical features

Of the 1009 patients recruited, the mean age was 50.0 years, 468 (46.4%) were recruited in Sheffield and 541 (53.6%) in Exeter; 727 (72.1%) were female and 282 (27.9%) were male. The index side was the left in 49.6% and the right in 50.4%. The figures for these characteristics based on the allocation group are shown in *Table 13* and for those who agreed to randomisation in *Table 14*. The significant differences between groups were that those presenting in Groups 1 and 2 included a higher proportion of female patients and were younger, and a significantly higher proportion of eligible patients were randomised in Sheffield than in Exeter (77.0% versus 18.7%).

The demographic and initial clinical features of patients in each of the final treatment groups are shown in *Table 15*. As would be expected on the basis of the criteria for selection, those in the mandatory observation group had a higher average BMI and a higher incidence of significant past medical history of coexisting disease.

Symptoms at presentation

The symptoms that were reported in the index leg and in the contra-lateral leg at the time of presentation are shown in *Table 16* for each of the clinical groups. Those undergoing mandatory observation reported a higher incidence of

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TABLE 14 *Demographics and clinical features of referrals by agreement to randomisation*

	Consent to randomisation	Declined randomisation	Mandatory observation	Total
N	357	426	226	1009
Sheffield:Exeter	278:79[a]	83:343[a]	107:119	468:541
Female:male	269:88	291:135	167:59	727:282
Age (SD) (years)	48.4 (13.0)	49.9 (14.0)	52.7 (12.9)	50.0 (13.5)
Height (SD) (cm)	167.1 (10.2)	168.4 (9.2)	166.6 (9.5)	167.6 (9.6)
BMI (SD)	26.4 (3.9)	25.3 (3.3)	30.7 (6.0)	26.8 (4.6)
Smokers	93 (26.1%)	85 (20.0%)	42 (18.6%)	220 (21.8%)
Family history of varicose veins	248 (69.5%)	307 (72.1%)	163 (72.1%)	718 (71.2%)
Family history of leg ulceration	38 (10.6%)	79 (18.5%)	40 (17.7%)	157 (15.6%)
Previous pregnancies (mean no.)	236 (2.1)	255 (1.7)	148 (2.3)	639 (2.0)

[a] $p < 0.05$, χ^2 test.

TABLE 15 *Demographics and clinical features of referrals by final treatment group*

	1	2	3	4	Total
N	34	77	246	652	1009
Sheffield:Exeter	23:11	65:12	190:56	190:462	468:541
Female:male	30:4	69:8	170:76	458:194	727:282
Age (SD) (years)	47.5 (12.5)	46.1 (13.2)	49.3 (13.0)	50.8 (13.7)	50.0 (13.5)
Height (SD) (years)	164.2 (7.8)	165.8 (8.5)	167.9 (10.9)	167.8 (9.3)	167.6 (9.6)
BMI (SD)	25.6 (4.8)	25.8 (3.8)	26.7 (3.8)	27.0 (5.0)	26.8 (4.6)
Smokers	10 (29.4%)	24 (31.2%)	59 (24.0%)	127 (19.5%)	220 (21.8%)
Family history of varicose veins	22 (64.7%)	49 (63.6%)	177 (72.0%)	470 (72.1%)	718 (71.2%)
Family history of leg ulceration	4 (11.8%)	5 (6.5%)	29 (11.8%)	119 (18.3%)	157 (15.6%)
Previous pregnancies (mean no.)	27 (2.2)	56 (2.0)	153 (2.1)	403 (1.9)	639 (2.0)

TABLE 16 *Symptoms reported at initial assessment by allocated group for index leg and second leg*

	Group1	Group 2	Group 3	Mandatory observation
N	64	183	536	226
Aching	59 (92.2%)	167 (91.3%)	451 (84.1%)	194 (85.8%)
Heaviness	39 (60.9%)	114 (62.3%)	296 (55.2%)	134 (59.3%)
Itching	34 (53.1%)	109 (59.6%)	315 (58.8%)	131 (58.0%)
Swelling	31 (48.4%)	83 (45.4%)	238 (44.4%)	127 (56.2%)
Relief from support	19 (29.7%)	58 (31.7%)	166 (31.0%)	76 (33.6%)
Cosmetic concerns	44 (68.8%)	122 (66.7%)	373 (69.6%)	154 (68.1%)
N	64	183	536	226
Any symptom[a]	19 (29.7%)	55 (30.1%)	222 (41.4%)	114 (50.4%)
Aching[a]	12 (18.8%)	47 (25.7%)	165 (30.8%)	84 (37.2%)
Heaviness	10 (15.6%)	36 (19.7%)	119 (22.2%)	67 (29.6%)
Itching[a]	8 (12.5%)	23 (12.6%)	109 (20.3%)	46 (20.4%)
Swelling	7 (10.9%)	19 (10.4%)	83 (15.5%)	47 (20.8%)
Relief from support[a]	4 (6.3%)	15 (8.2%)	80 (14.9%)	42 (18.6%)
Cosmetic concerns	15 (23.4%)	43 (23.5%)	150 (28.0%)	78 (34.5%)

[a] $p < 0.05$, χ^2 test.

TABLE 17 *Reflux present on examination with HHD by treatment arm for LSV reflux and popliteal reflux*

	Randomised	Declined randomisation	Total
LSV reflux			
Group 1	3/34 (8.8%)	0/30 (0.0%)	3/64 (4.7%)
Group 2	60/77 (77.9%)	85/106 (80.2%)	145/183 (79.2%)
Group 3	217/246 (88.2%)	252/290 (86.9%)	469/536 (87.5%)
Mandatory observation			182/226 (80.5%)
Total			799/1009 (79.2%)
Popliteal reflux			
Group 1	2/34 (5.9%)	0/30 (0.0%)	2/64 (3.1%)
Group 2	10/77 (13.0%)	34/106 (32.1%)	44/183 (24.0%)
Group 3	37/246 (15.0%)	45/290 (15.5%)	82/536 (15.3%)
Mandatory observation			52/226 (23.0%)
Total			180/1009 (17.8%)

swelling, otherwise there were no significant differences between the various groups. There was a higher incidence of contra-lateral symptoms in those with more extensive varicose veins, with those in the mandatory observation group having the highest incidence (50.4%) of symptoms in the second leg ($p < 0.05$, χ^2 test for trend).

Anatomical extent

Based on the anatomical classification described in Chapter 3, the extent of veins was classified on a 10-point scale from 0 to 9, with 0 representing no visible veins and 9 being the most extensive veins (i.e. veins >5 mm in diameter in both the upper and lower thigh and in all four quadrants of the lower leg). Overall, 25.3% of patients had varicosities in the upper thigh, 67.3% in the lower thigh and 97.3% in the BK area of the index limb, with the comparable figures for the second limb being 7.6, 26.3 and 37.5%, respectively. BK varicosities affected three or more segments in 23.5% of index limbs and 5.5% of second limbs.

Relationship between symptoms and anatomical distribution of veins

Figure 5 shows the relationship between the extent of veins and the presence of the main symptoms of aching, heaviness, itching, swelling and cosmetic concerns. There was a small but significant difference in that more aching was reported in those with less extensive veins and more itching in those with more extensive veins. There was no relationship between the presence of other symptoms and anatomical extent.

Superficial venous reflux

At the time of initial assessment, all patients were examined with an HHD for the presence of reflux at the groin, in the LSV above the knee and in the popliteal fossa. Overall, 799 patients (79.2%) were found to have reflux in the long saphenous system, with 550 (68.8%) having reflux at both the groin and in the LSV above the knee, 168 (21.0%) identified at the groin only and 81 (10.1%) identified only in the LSV above the knee. A total of 180 patients (17.8%) had reflux identified in the popliteal fossa. The breakdown of these figures for the trial groups is shown in *Table 17*. There is a positive correlation between the extent of varicose veins and the finding of reflux at the groin (*Figure 6*).

As part of the trial protocol, duplex scans were carried out in the laboratory in all patients. These were blinded to the clinician assessing the patient unless there was a clinical indication for a scan to be requested. Scans were requested in 352 patients (34.9%), with the most common reason for such requests being the suspicion of incompetence at the popliteal fossa, which was responsible for 50.6% of scans (*Table 18*).

TABLE 18 *Reasons for requesting scans (index legs)*

	No.
Total (index legs)	1009
Scan indicated	352 (34.9%)
Suspicion of popliteal reflux	178 (17.6%)
Recurrence	67 (6.6%)
Atypical distribution	84 (8.3%)
History of DVT/ulcer, etc.	63 (6.2%)

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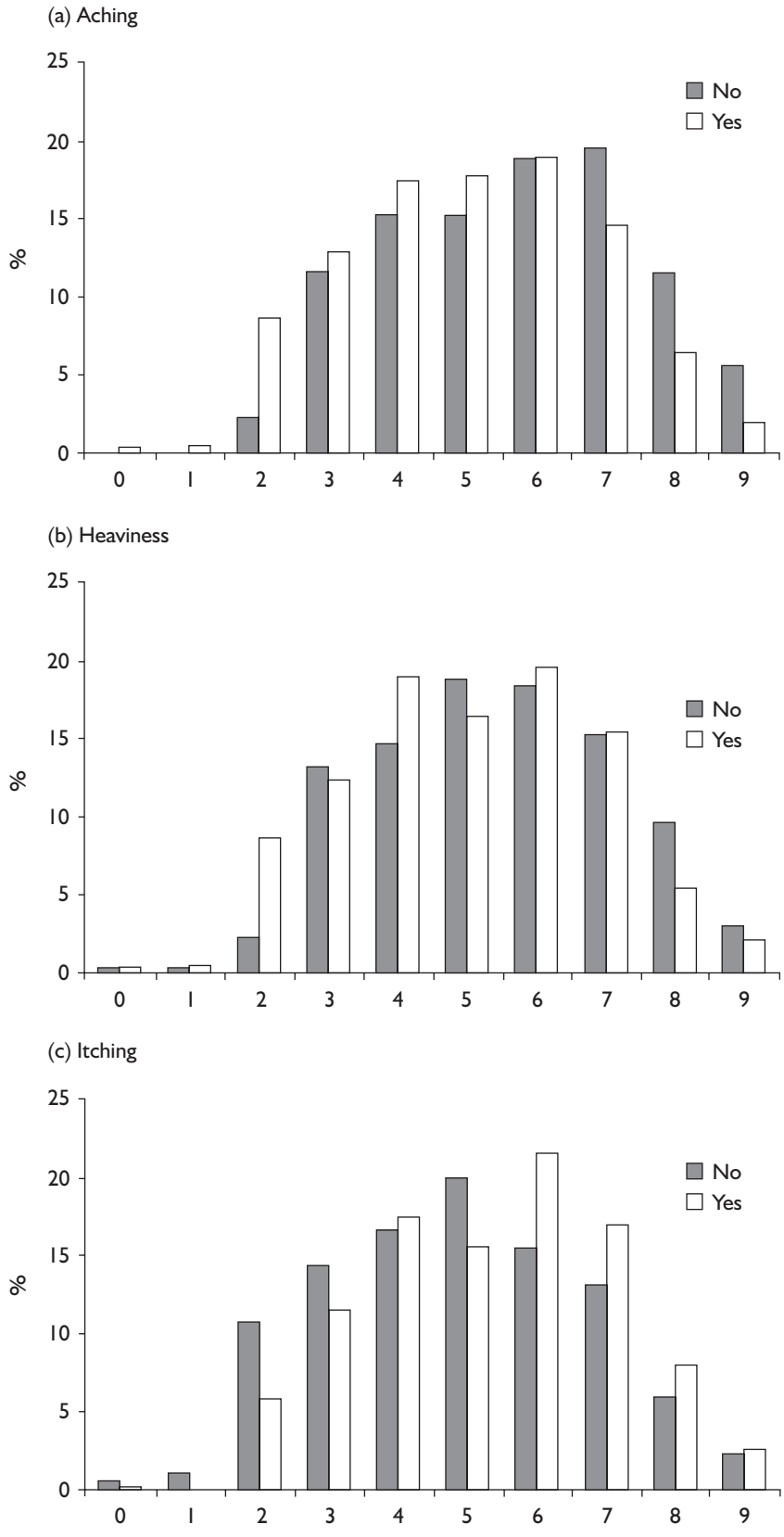

FIGURE 5 *Relationship between extent of varicose veins and presence of symptoms: proportion (%) in each anatomical category as defined in* Table 7

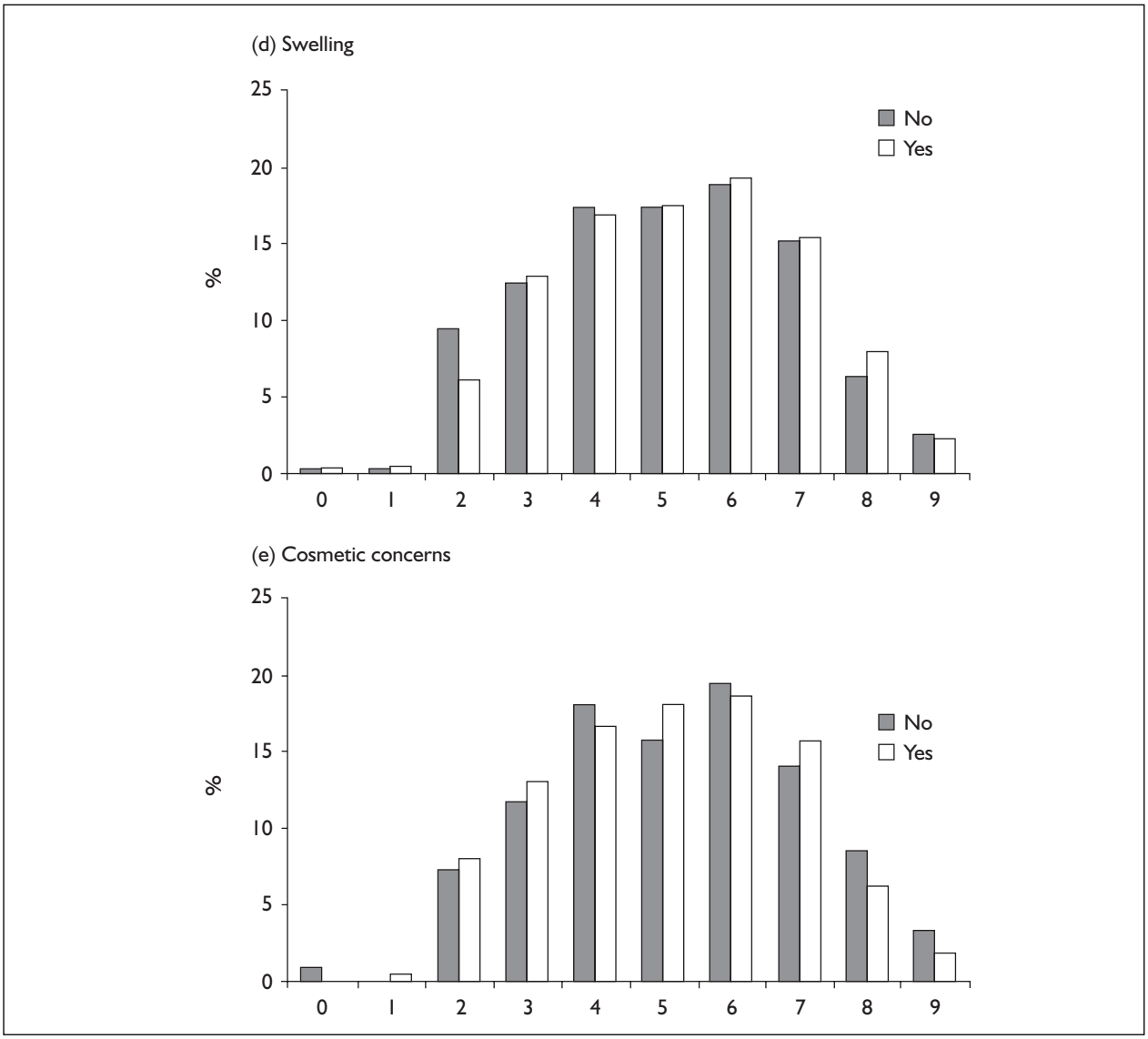

FIGURE 5 (cont'd) *Relationship between extent of varicose veins and presence of symptoms: proportion (%) in each anatomical category as defined in* Table 7

Key points

- A total of 1841 patients were referred in a period of 2 years (equivalent to about 100 patients per 100,000 of population per year).
- About 14% of patients failed to attend their first outpatient appointment.
- Of those suitable for randomisation, the majority (68%) were clinically in Group 3, 23% in Group 2 and 8% in Group 1.
- Of those who were eligible, 45% agreed to be randomised.
- There was a significant difference between the two trial centres in the proportion agreeing to randomisation.
- Almost all patients reported some symptoms, with the most common symptoms being aching, cosmetic problems, heaviness and itching. Approximately 14% of patients reported bilateral symptoms.
- On examination with an HHD, 80% of patients were thought to have saphenofemoral incompetence in the index limb and 18% of patients to have some popliteal reflux.
- There was a small but significant correlation between anatomical extent and some symptoms, with aching being associated with less extensive and itching with more extensive varicose veins. No correlation was identified between other symptoms and the anatomical extent of the varicose veins.
- The proportion of patients eligible for the Group 1 trial was small, with only 34 patients agreeing to randomisation.

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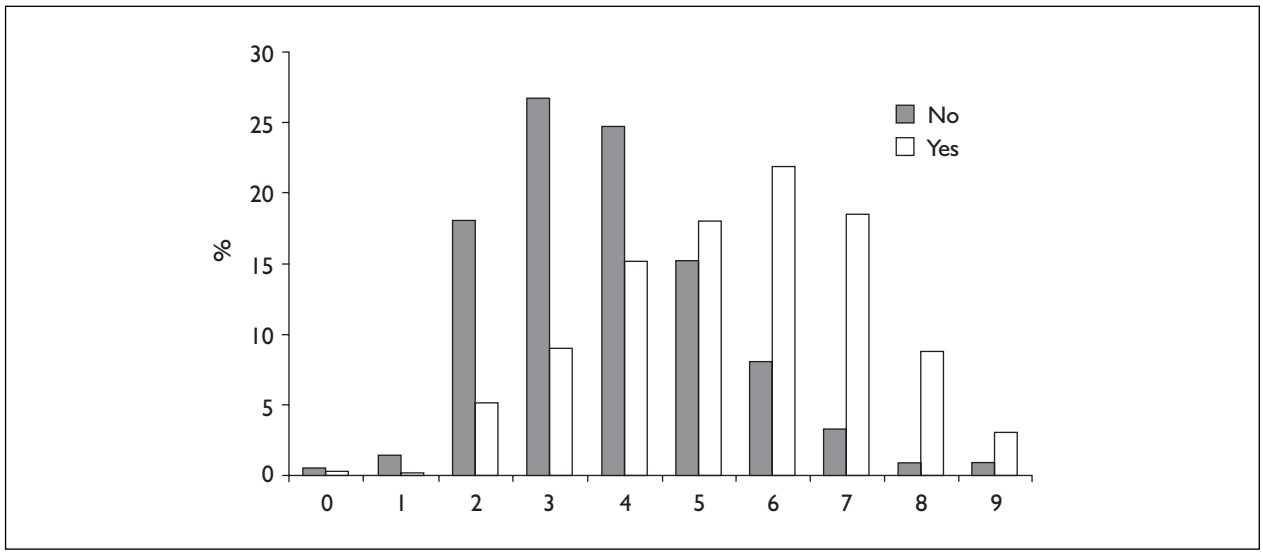

FIGURE 6 *Anatomical extent of varicose veins for all patients with and without reflux in the long saphenous vein, as demonstrated with HHD: proportion (%) in each anatomical category as defined in* Table 7

TABLE 19 *Demographics and clinical features of Group 1 patients by result of randomisation*

	Randomised to conservative treatment	Randomised to sclerotherapy	All randomised patients	Declined randomisation	Total
N	18	16	34	30	64
Sheffield:Exeter	1 :4	9:7	23:11[a]	8:22[a]	31:33
Female:male	16:2	14:2	30:4	24:6	54:10
Age (SD) (years)	46.6 (11.3)	48.6 (14.0)	47.5 (12.5)	45.5 (13.1)	46.5 (12.7)
Height (SD) (cm)	165.4 (8.3)	162.9 (7.3)	164.2 (7.8)	167.2 (8.0)	165.7 (8.0)
BMI (SD)	26.0 (3.7)	25.1 (5.8)	25.6 (4.8)	24.2 (3.7)	24.9 (4.3)
Smokers	5 (27.8%)	5 (31.3%)	10 (29.4%)	6 (20.0%)	16 (25.0%)
Family history of varicose veins	10 (55.6%)	12 (75.0%)	22 (64.7%)	23 (76.7%)	45 (70.3%)
Family history of leg ulceration	4 (22.2%)	0 (0.0%)	4 (11.8%)	7 (23.3%)	11 (17.2%)
Previous pregnancies (mean no.)	14 (2.3)	13 (2.1)	27 (2.2)	19 (2.0)	46 (2.1)

[a] $p < 0.05$, χ^2 test.

Group 1 trial

Recruitment, treatments and follow-up

Of the 64 patients identified as being in Group 1 who were available for randomisation, 34 (53%) agreed to be randomised between conservative treatment and sclerotherapy. Randomisation resulted in 18 patients allocated to conservative treatment and 16 to sclerotherapy. The demographic details for these patients are shown in *Table 19*. A greater proportion of patients were randomised in Sheffield than in Exeter (74% versus 33%). There were no other significant differences in demographic or clinical features between those who consented or declined randomisation or between the two arms of the RCT.

A summary of the treatment allocation and follow-up in this trial, in keeping with the format suggested by the CONSORT statement,[139] is shown in *Figure 7*.

Complications

Information was collected on self-reported complications, additional visits to GPs, nurses and hospital and through direct questioning on specific complications. In the conservative arm of the trial, one patient (6.6%) reported phlebitis in the first year after treatment, but no other complications relating to varicose veins were reported.

In the sclerotherapy arm of the randomised trial, one patient (7.1%) reported blistering and

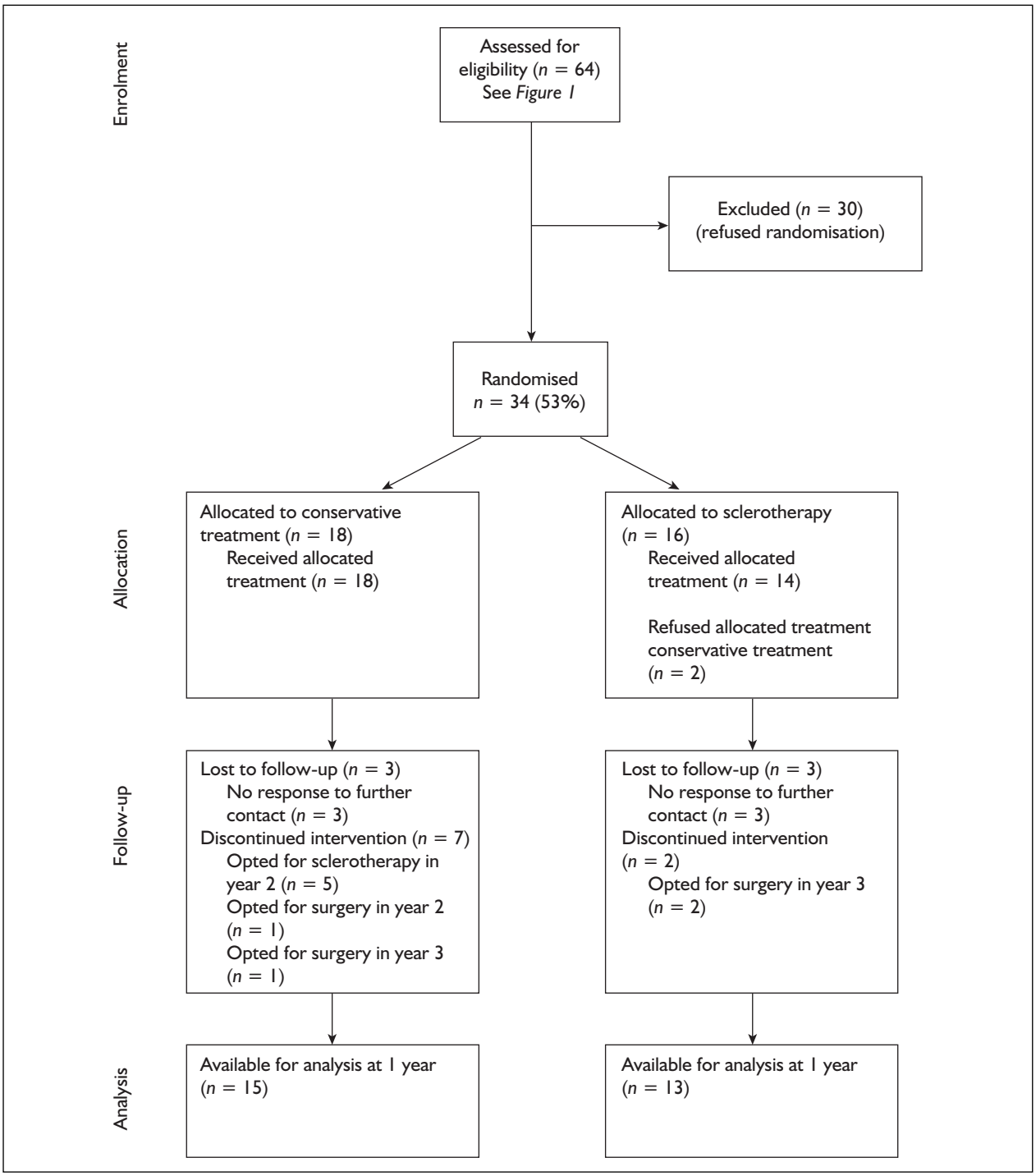

FIGURE 7 *Outcome for Group 1 patients*

ulceration at the site of injection, which had settled by 6 weeks without scarring. Two patients (15.4%) reported phlebitis, one of whom required a visit to the GP. There were no other contacts with health professionals within the first year, other than those planned for treatment regarding varicose veins. One patient (7.7%) reported troublesome staining following sclerotherapy, and on direct questioning five others (38%) noted staining, although this had not been specifically volunteered as a complication or problem.

In the Group 1 patients who had declined randomisation, two (6.7%) of those treated conservatively had seen their GP, one for pins and needles in the leg, which they related to the varicose veins, and one for the development of

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new varicose veins. None of the patients who elected to undergo surgery or sclerotherapy outside the RCT spontaneously reported any further complications, although, on direct questioning, three (23%) of those undergoing sclerotherapy reported staining and two (26%) of those undergoing surgery reported numbness.

Symptoms

The main symptoms reported at the initial assessment are shown in *Table 20*. The most common symptom was aching, reported by 92.2% of patients, followed by cosmetic concerns (68.8%), heaviness (60.9%), itching (53.1%) and swelling (48.4%). Some patients reported relief of symptoms through the use of compression hosiery (29.7%). There were no significant differences between those who did or did not agree to randomisation or between the arms of the randomised trial.

The same symptoms were assessed at the 1-year follow-up, and *Table 21* shows the number of patients reporting that the symptoms were better, the same or worse. With sclerotherapy, the majority of patients (84.6%) had no cosmetic concerns or considered that there had been cosmetic improvement, compared with 14.3% of those undergoing conservative treatment (significant, $p < 0.05$, χ^2 test for trend). Sclerotherapy also resulted in significantly better results for aching. The results for other symptoms were not statistically significant, and the number of patients available for follow-up at 2 years was too small to draw valid conclusions.

The symptoms reported by those patients who declined randomisation are shown in *Table 22*.

Anatomical extent and progression

The anatomical extent of varicose veins was assessed by a clinician at the time of recruitment to the trial and at the 1-year follow-up. There were no significant differences between anatomical extent of the groups at baseline. *Figure 8* shows the anatomical extent at baseline and at 1 year in those undergoing conservative treatment and sclerotherapy. There was an improvement in the anatomical extent in 11 of 13 patients (84.6%) undergoing sclerotherapy, compared with four (28.6%) of those undergoing conservative treatment ($p < 0.05$, χ^2 test for trend). The progress of varicose veins was assessed at 2 and 3 years through the questionnaire, with patients reporting on the development of new veins and the appearance of the index leg. Ten out of 13 patients responding at 2 years (76.9%) reported the development of new veins, with no significant difference between the arms of the trial, and of those reporting on appearance, 5 of 13 (38.5%) felt there had been an improvement and three (23.1%) felt there had been deterioration. There

TABLE 20 *Symptoms at initial assessment of Group 1 patients by result of randomisation*

	Randomised to conservative treatment	Randomised to sclerotherapy	All randomised patients	Declined randomisation	Total
N	18	16	34	30	64
Aching	15 (83.3%)	16 (100.0%)	31 (91.2%)	28 (93.3%)	59 (92.2%)
Heaviness	9 (50.0%)	11 (68.8%)	20 (58.8%)	19 (63.3%)	39 (60.9%)
Itching	10 (55.6%)	10 (62.5%)	20 (58.8%)	14 (46.7%)	34 (53.1%)
Swelling	9 (50.0%)	6 (37.5%)	15 (44.1%)	16 (53.3%)	31 (48.4%)
Cosmetic concerns	15 (83.3%)	11 (68.8%)	26 (76.5%)	18 (60.0%)	44 (68.8%)

TABLE 21 *Symptoms reported as better, the same or worse at 1-year assessment in randomised arms of Group 1 trial*

	Conservative				Sclerotherapy			
	None	Better	Same	Worse	None	Better	Same	Worse
Aching[a]	2 (14%)	2 (14%)	6 (43%)	4 (29%)	4 (31%)	5 (38%)	3 (23%)	1 (8%)
Heaviness	6 (43%)	0 (0%)	6 (43%)	2 (14%)	10 (77%)	1 (8%)	1 (8%)	1 (8%)
Itching	5 (36%)	2 (14%)	6 (43%)	1 (7%)	9 (69%)	2 (15%)	1 (8%)	1 (8%)
Swelling	8 (57%)	0 (0%)	5 (36%)	1 (7%)	10 (77%)	1 (8%)	1 (8%)	1 (8%)
Cosmetic concerns[a]	1 (7%)	1 (7%)	7 (50%)	5 (36%)	4 (31%)	7 (54%)	1 (8%)	1 (8%)

[a] $p < 0.05$, χ^2 test for trend.

TABLE 22 *Symptoms reported as better, the same or worse at 1-year assessment in those who declined randomisation in Group 1 trial*

	None	Better	Same	Worse
Aching	7 (39%)	7 (39%)	3 (17%)	1 (6%)
Heaviness	6 (33%)	3 (17%)	1 (6%)	1 (6%)
Itching	13 (72%)	4 (22%)	1 (6%)	0 (0%)
Swelling	4 (22%)	3 (17%)	0 (0%)	0 (0%)
Cosmetic concerns	8 (44%)	6 (33%)	3 (17%)	1 (6%)

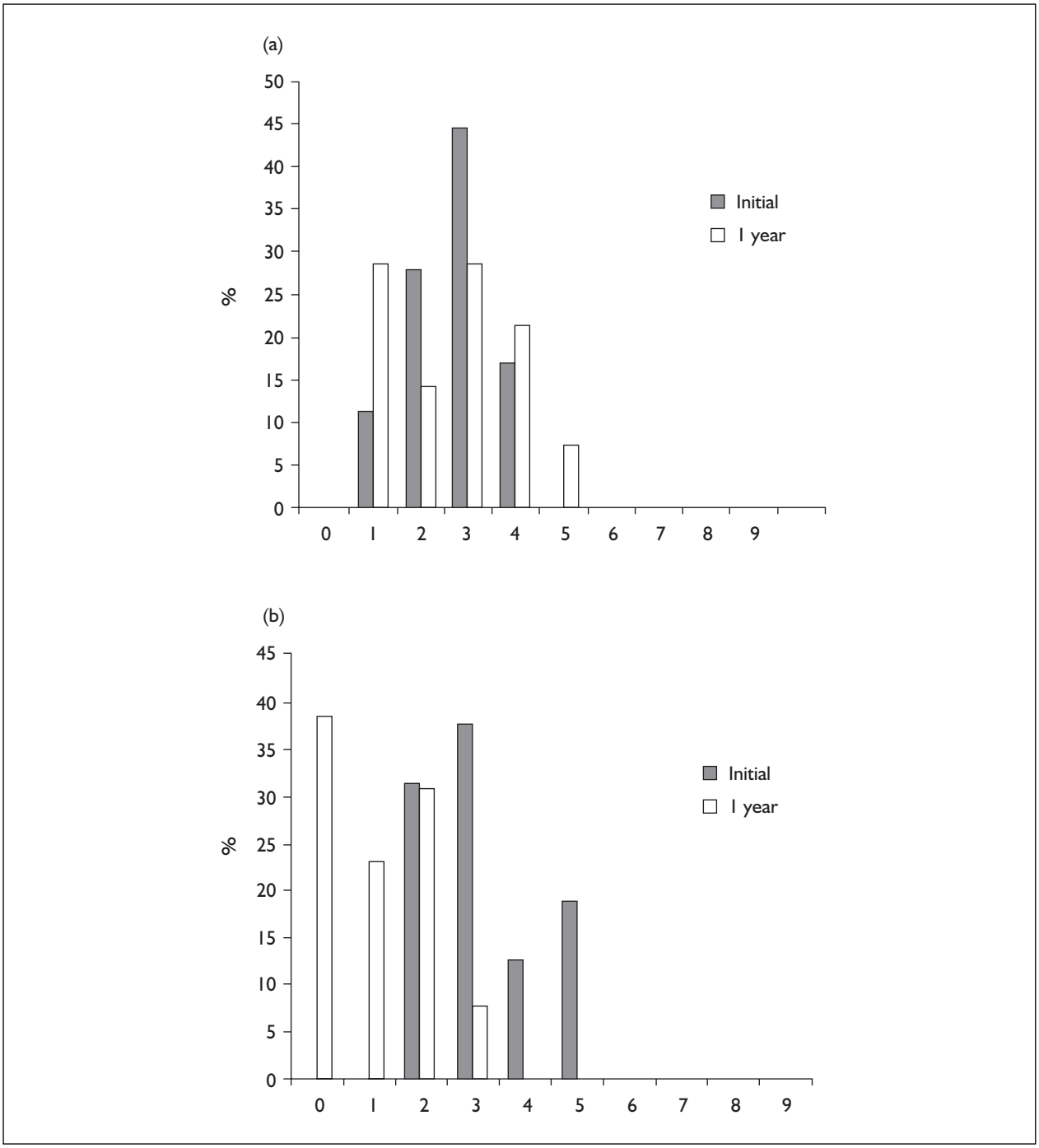

FIGURE 8 *Anatomical extent at baseline and 1-year assessment for patients in Group 1 randomised to (a) conservative treatment and (b) sclerotherapy: proportion (%) in each anatomical category as defined in* Table 7

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TABLE 23 *Quality of life outcomes for Group 1 trial (no significant differences)*

	Baseline		1 year		2 years	
	Conservative	**Sclerotherapy**	**Conservative**	**Sclerotherapy**	**Conservative**	**Sclerotherapy**
SF-6D	0.73 (0.09) *n* = 17	0.71 (0.11) *n* = 15	0.74 (0.07) *n* = 15	0.72 (0.16) *n* = 13	0.71 (0.12) *n* = 6	0.67 (0.16) *n* = 5
EQ-5D	0.76 (0.19) *n* = 18	0.77 (0.13) *n* = 16	0.72 (0.28) *n* = 15	0.82 (0.27) *n* = 12	0.81 (0.11) *n* = 5	0.84 (0.17) *n* = 5
VAS	0.77 (0.13) *n* = 18	0.78 (0.18) *n* = 16	0.81 (0.14) *n* = 15	0.75 (0.22) *n* = 12	0.77 (0.19) *n* = 5	0.78 (0.22) *n* = 6
SG	0.94 (0.11) *n* = 13	0.95 (0.13) *n* = 14	0.90 (0.27) *n* = 13	1.00 (0.01) *n* = 13		

The figures in parentheses are the standard deviation.
SG, standard gamble.

were not sufficient numbers of responses to draw conclusions regarding differences between the treatment arms.

Quality of life

Full details of the HRQoL outcomes are provided in Chapter 5. A summary of the primary end-point of average utility based on the index derived from the SF-36 data is shown in *Table 23* alongside the other HRQoL measures derived from the EQ-5D, the VAS and the standard gamble. None of the differences between treatment arms reached statistical significance.

Patient satisfaction

At the 1-year follow-up, eight of 14 patients (57.1%) of those randomised to conservative treatment were unhappy with their treatment and many of these requested sclerotherapy or surgery. Of those randomised to sclerotherapy, only one patient (7.7%, $p < 0.05$, Fisher's exact test) was dissatisfied with the treatment as she felt that there had been no improvement and new veins had appeared with a worsening of symptoms.

Key points

- The proportion of patients eligible for the Group 1 trial was small, with only 34 patients agreeing to randomisation.
- Patients in Group 1 tended to be younger and included a higher proportion of females.
- No serious complications were observed in either arm of the trial.
- The symptoms of cosmetic problems and aching and the anatomical extent of varicose veins were significantly improved in the sclerotherapy group at 1 year compared with the conservative arm of the trial.
- Those who underwent sclerotherapy were more likely to be satisfied at 1 year, compared with those treated conservatively.
- There were no significant differences in HRQoL scores at 1 year, but the sample size was insufficient to exclude a clinically significant difference.

Group 2 trial

Recruitment, treatments and follow-up

Of 183 patients who were identified as Group 2 on initial assessment, 106 declined to be randomised. The remaining 77 patients were randomised with 41 being allocated to sclerotherapy and 36 to surgery. Demographic and clinical features are shown in *Table 24*. Once again a significantly smaller proportion of those in Exeter consented to randomisation (12.4% versus 75.6%). There were significantly more males (26.4% versus 10.4%, $p < 0.05$, χ^2 test), fewer smokers (17.0% versus 31.2%, $p < 0.05$, χ^2 test) and more with a family history of leg ulcers (20.8% versus 6.5%, $p < 0.05$, χ^2 test) amongst those who declined randomisation. There were no significant differences between the treatment arms within the randomised trial.

A summary of the treatment allocation and follow-up in this trial, in keeping with the format suggested by the CONSORT statement,[139] is shown in *Figure 9*.

Complications

The complications are summarised in *Table 25*. Amongst those patients randomised to sclerotherapy, there was one (2.4%) who developed

TABLE 24 *Demographics and clinical features of Group 2 patients by result of randomisation*

	Randomised to sclerotherapy	Randomised to surgery	All randomised patients	Declined randomisation	Total
N	41	36	77	106	183
Sheffield:Exeter	35:6	30:6	65:12[a]	21:85[a]	86:97
Female:male	38:3	31:5	69:8	78:28	14 :36
Age (SD) (years)	47.0 (13.5)	45.1 (12.9)	46.1 (13.2)	47.1 (14.1)	46.7 (13.7)
Height (SD) (cm)	164.6 (8.2)	167.1 (8.8)	165.8 (8.5)	167.5 (8.9)	166.8 (8.7)
BMI (SD)	25.5 (3.4)	26.3 (4.2)	25.8 (3.8)	25.5 (3.4)	25.6 (3.5)
Smokers	12 (29.3%)	12 (33.3%)	24 (31.2%)	18 (17.0%)[a]	42 (23.0%)
Family history of varicose veins	29 (70.7%)	20 (55.6%)	49 (63.6%)	78 (73.6%)	127 (69.4%)
Family history of leg ulceration	2 (4.9%)	3 (8.3%)	5 (6.5%)[a]	22 (20.8%)[a]	27 (14.8%)
Previous pregnancies (mean no.)	33 (2.0)	23 (1.9)	56 (2.0)	68 (1.7)	124 (1.8)

[a] $p < 0.05$, χ^2 test for trend.

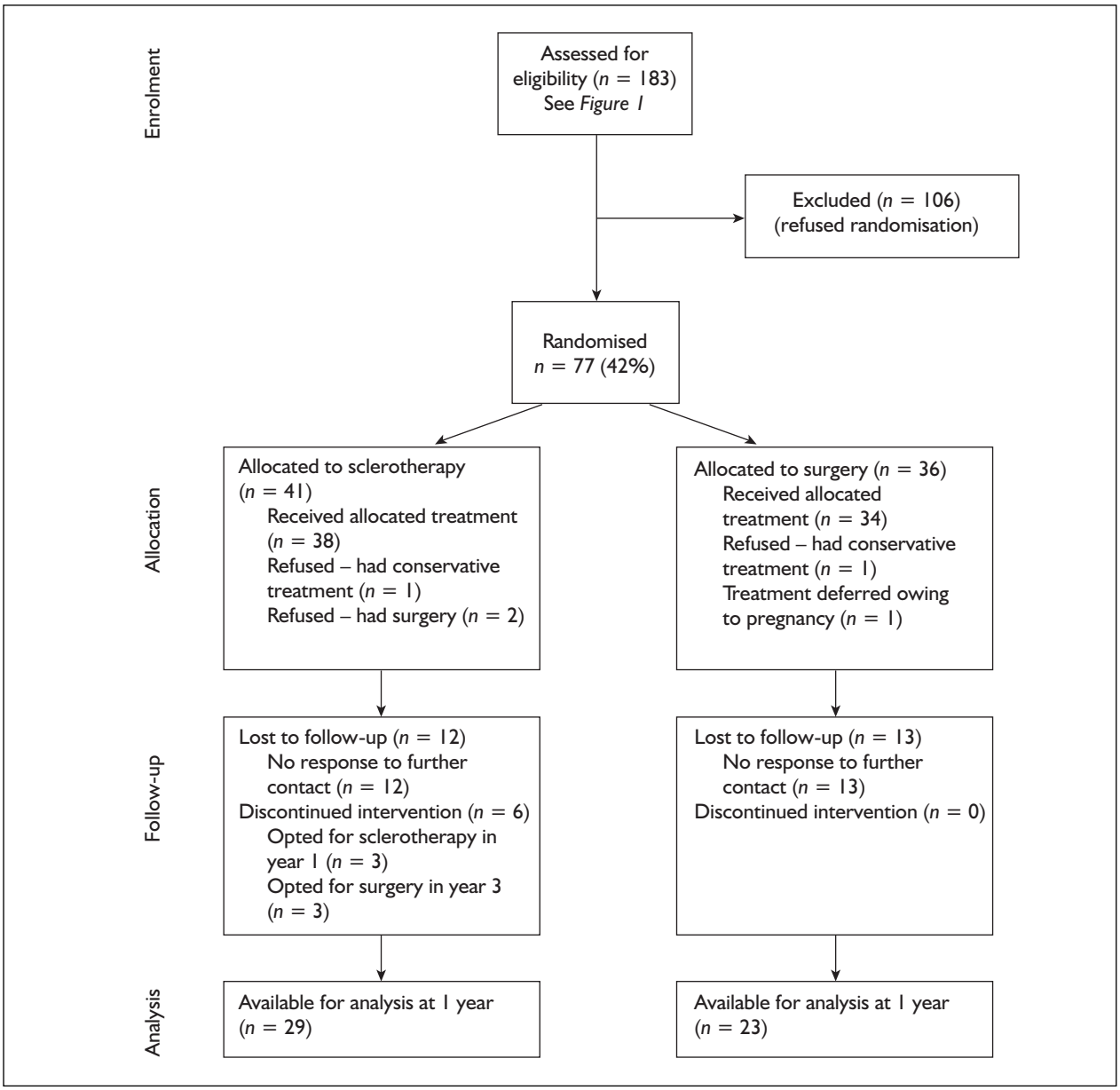

FIGURE 9 *Outcome for Group 2 patients*

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TABLE 25 *Summary of complications in Group 2*

Complication	No. (%)	Comments
Randomised to sclerotherapy		
Pain	1 (2.4)	
Further sclerotherapy required	1 (2.4)	
Wound problems	1 (2.4)	Patient who crossed over to surgical treatment
Phlebitis in first year	2 (6.9)	
Staining	15 (37)	No spontaneous reports, these reported on direct questioning
Randomised to surgery		
Allergy	2 (5.6)	One to skin preparation, one to adhesive bandages
Urinary retention	1 (2.8)	Required overnight stay following day-case surgery
Tight bandage	1 (2.8)	Returned to A&E for rebandaging
Wound infection	1 (2.8)	
Non-randomised		
DVT	1	2 weeks after surgery
Chest infection	1	Readmitted to hospital 5 days after surgery
Wound infection	3	One requiring readmission and abscess drainage
Blistering after sclerotherapy	1	
Phlebitis in first year	1	

a small ulcer at the site of sclerotherapy, one (2.4%) who attended their GP for pain shortly after the procedure, one (2.4%) who underwent a second set of sclerotherapy injections and one (2.4%) who visited their GP on one occasion for removal of a retained suture following cross-over to surgery. Two (6.9%) reported phlebitis and four others (13.8%) visited their GP in relation to their varicose veins in the first year. There were no other additional visits to the hospital relating to varicose veins.

Amongst those randomised to surgical treatment, two (5.6%) reported skin allergy, one (2.8%) developed postoperative urinary retention, one (2.8%) developed a wound infection and one (2.8%) needed the leg re-bandaged. In total, this group of patients had three visits to a GP, one visit to a district nurse, one unplanned admission to hospital and one attendance at Accident and Emergency relating to their varicose veins in the first year of treatment.

Of the 106 patients who declined randomisation, 22 were treated conservatively, 10 by sclerotherapy and 74 underwent surgical treatment. One patient was admitted to hospital with a DVT 2 weeks after surgical treatment and was subsequently anti-coagulated with warfarin for 3 months, a second patient was admitted to hospital 5 days postoperatively, with pleuritic chest pain, thrombo-embolic disease was excluded and a chest infection was treated with antibiotics. Three patients reported wound infection, one of these having a hospital admission for incision and drainage of an abscess on two occasions (4 and 6 weeks following the operation). The other two patients had a single visit to their GP and were treated with antibiotics.

In addition to the self-reported complications, staining was present at 1 year in 15 of 41 patients randomised to sclerotherapy, and in those randomised to surgery two reported staining and seven reported numbness, although none of these was thought to be a significant problem by the patient concerned.

Symptoms

The symptoms reported at the initial assessment are shown in *Table 26*. The most commonly reported symptoms were aching (91.3%), followed by cosmetic problems (66.7%), heaviness (62.3%), itching (59.6%) and swelling (45.4%). Relief of symptoms through the use of compression hosiery was reported in 31.7% of patients. There were no significant differences between the prevalence of these symptoms in those who were randomised and those who declined randomised, or between the two arms of the RCT.

The majority of patients on both treatments reported that all symptoms were improved or absent at the 1-year follow-up (see *Table 27*). There were no statistically significant differences between the two treatment arms in this respect.

TABLE 26 *Symptoms at initial assessment of Group 2 patients by result of randomisation*

	Randomised to sclerotherapy	Randomised to surgery	All randomised patients	Declined randomisation	Total
N	41	36	77	106	183
Aching	37 (90.2%)	32 (88.9%)	69 (89.6%)	98 (92.5%)	167 (91.3%)
Heaviness	25 (61.0%)	22 (61.1%)	47 (61.0%)	67 (63.2%)	114 (62.3%)
Itching	21 (51.2%)	20 (55.6%)	41 (53.2%)	68 (64.2%)	109 (59.6%)
Swelling	19 (46.3%)	15 (41.7%)	34 (44.2%)	49 (46.2%)	83 (45.4%)
Cosmetic concerns	27 (65.9%)	27 (75.0%)	54 (70.1%)	68 (64.2%)	122 (66.7%)

TABLE 27 *Symptoms reported as better, the same or worse at 1-year assessment in randomised arms of Group 2 trial*

	Sclerotherapy				Surgery			
	None	Better	Same	Worse	None	Better	Same	Worse
Aching	5 (18%)	10 (36%)	10 (36%)	3 (11%)	5 (20%)	12 (48%)	6 (24%)	2 (8%)
Heaviness	9 (32%)	9 (32%)	10 (36%)	0 (0%)	10 (40%)	10 (40%)	3 (12%)	2 (8%)
Itching	13 (46%)	6 (21%)	7 (25%)	2 (7%)	13 (52%)	8 (32%)	2 (8%)	2 (8%)
Swelling	17 (61%)	3 (11%)	7 (25%)	1 (4%)	17 (68%)	5 (20%)	2 (8%)	1 (4%)
Cosmetic concerns	7 (25%)	9 (32%)	8 (29%)	4 (14%)	5 (20%)	15 (60%)	1 (4%)	4 (16%)

TABLE 28 *Symptoms reported as better, the same or worse at 1-year assessment in those who declined randomisation in Group 2 trial*

	None	Better	Same	Worse
Aching[a]	25 (40%)	28 (45%)	5 (8%)	4 (6%)
Heaviness[a]	39 (63%)	21 (34%)	1 (2%)	1 (2%)
Itching[a]	40 (65%)	18 (29%)	1 (2%)	3 (5%)
Swelling	42 (68%)	10 (16%)	7 (11%)	3 (5%)
Cosmetic concerns	23 (37%)	23 (37%)	10 (16%)	6 (10%)

[a] $p < 0.05$, χ^2 test for trend compared with all randomised patients.

The symptoms reported in those patients who declined randomisation are shown in *Table 28*. Compared to all randomised patients, those who declined randomisation reported greater rates of improvement in the symptoms of aching, heaviness and itching ($p < 0.05$, χ^2 test for trend).

Anatomical extent and progression

There was no difference in anatomical extent between treatment arms at baseline, but those who declined randomisation had significantly more extensive varicosities ($p < 0.05$, χ^2 test for trend). The comparison between extent of veins at baseline and 1-year follow-up is shown in *Figure 10* for those patients in the randomised arms allocated to sclerotherapy or surgery. Following surgical treatment, 76% of patients had no visible varicosities at 1-year follow-up, compared with 39% following sclerotherapy ($p < 0.05$, χ^2 test).

The development of new varicose veins was reported by six of 53 (11.3%) patients at 1 year, eight of 32 patients (25%) at 2 years and 12 of 17 patients (17.6%) at 3 years. There were no significant differences between surgery and sclerotherapy in respect to these figures. In terms of appearance, at 2 years four of 14 patients (29%) who had undergone sclerotherapy and two of 18 patients (11%) following surgery felt that their legs were the same or worse compared with prior treatment (not significant).

Quality of life

Summary results for the HRQoL outcomes are shown in *Table 29*. Based on the primary end-point of the utility derived from the SF-36 value at 1 year, those patients randomised to surgery had an increased utility of 0.76 versus 0.71 for those randomised to sclerotherapy, which did not reach

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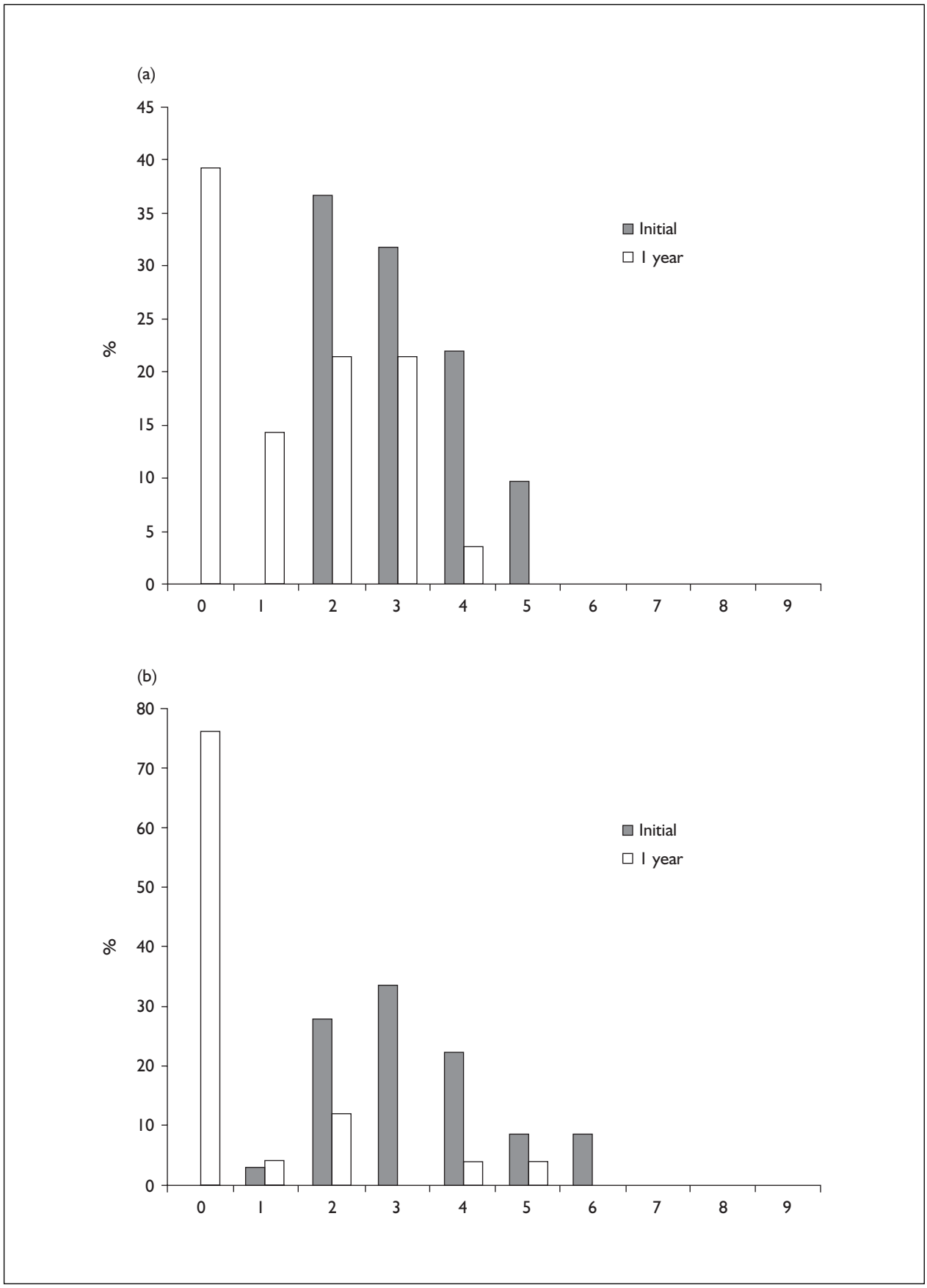

FIGURE 10 *Anatomical extent at baseline and 1-year assessment for patients in Group 2 randomised to (a) sclerotherapy and (b) surgery: proportion (%) in each anatomical category as defined in* Table 7

TABLE 29 *Quality of life outcomes for Group 2 trial*

	Baseline		1 year		2 years	
	Sclerotherapy	**Surgery**	**Sclerotherapy**	**Surgery**	**Sclerotherapy**	**Surgery**
SF-6D	0.69 (0.10) *n* = 34	0.71 (0.09) *n* = 31	0.71 (0.11) *n* = 28	0.76 (0.10) *n* = 24	0.75 (0.11) *n* = 15	0.76 (0.11) *n* = 16
EQ-5D	0.71 (0.21) *n* = 34	0.79 (0.14) *n* = 30	0.80 (0.14)* *n* = 28	0.85 (0.20)* *n* = 22	0.74 (0.11) *n* = 6	0.84 (0.32) *n* = 10
VAS	0.75 (0.16) *n* = 36	0.74 (0.15) *n* = 32	0.77 (0.18)* *n* = 27	0.83 (0.14)* *n* = 22	0.77 (0.13) *n* = 7	0.83 (0.13) *n* = 10
SG	0.89 (0.15) *n* = 28	0.93 (0.14) *n* = 30	0.95 (0.13) *n* = 24	0.90 (0.23) *n* = 22		

Values in parentheses are the standard deviation.
* Significant difference ($p < 0.05$) for sclerotherapy vs surgery.
SG, standard gamble.

statistical significance. Significant differences in utility were present at 1-year follow-up for the EQ-5D and VAS measures ($p < 0.05$, paired *t*-test). More detailed analysis of the HRQoL data is provided in Chapter 5.

Patient satisfaction

At the 1-year follow up, four of 28 patients (14.3%) undergoing sclerotherapy and four of 25 patients (16%) undergoing surgery were dissatisfied with their initial treatment (not significant), with three of these sclerotherapy patients electing to have surgical treatment.

Key points

- A total of 183 patients were identified as Group 2, of whom 77 consented to randomisation.
- There were no major complications in the randomised trial. However two of the patients who declined randomisation and underwent surgery developed major complications (one DVT and one chest infection).
- There were no significant differences between surgery and sclerotherapy with respect to changes in symptoms at 1 year.
- Those who declined randomisation had improved outcomes at 1 year for aching, heaviness and itching, compared with those who participated in the RCT.
- Surgical treatment was significantly more likely to result in improved anatomical clearance of the varicose veins.
- Surgery resulted in improved HRQoL at 1 year on EQ-5D and VAS measures compared with sclerotherapy.
- There was no significant difference in patient satisfaction at 1 year.

Group 3 trial

Recruitment, treatments and follow-up

There were 536 patients who were identified as being Group 3 on the basis of the initial assessment. Of these, 290 (54%) declined to be randomised, leaving 246 patients, of whom 122 were randomised to conservative treatment and 124 to surgery.

Of all the patients identified as Group 3, 359 (67.0%) were female and 177 (33.0%) male, and the average age was 50.4 years. Other demographic and clinical features are shown in *Table 30*. A significantly smaller proportion of those in Exeter than in Sheffield consented to randomisation (19.2% versus 77.9%). There were no other significant differences, either between those who agreed to randomisation and those who declined, or between the treatment arms amongst those who were randomised.

A summary of the treatment allocation and follow-up in this trial, in keeping with the format suggested by the CONSORT statement,[139] is shown in *Figure 11*.

Complications

The complications are summarised in *Table 31*. Amongst those patients who were randomised to conservative treatment, three (1.0%) reported phlebitis and two others (0.7%) had seen their GP in the first year, one for a dry rash on the leg and one regarding leg swelling. Of those who crossed over to surgical treatment, one had seen their GP regarding wound infection and one had seen a practice nurse regarding bruising. There were no other visits to the

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TABLE 30 *Demographics and clinical features of Group 3 patients by result of randomisation*

	Randomised to conservative treatment	Randomised to sclerotherapy	All randomised patients	Declined randomisation	Total
N	122	124	246	290	536
Sheffield:Exeter	92:30	98:26	190:56[a]	54:236[a]	244:292
Female:male	87:35	83:41	170:76	189:101	359:177
Age (SD) (years)	49.5 (13.5)	49.0 (12.5)	49.3 (13.0)	51.3 (13.8)	50.4 (13.5)
Height (SD) (cm)	168.0 (9.9)	167.8 (11.8)	167.9 (10.9)	168.8 (9.4)	168.4 (10.1)
BMI (SD)	26.9 (4.1)	26.4 (3.5)	26.7 (3.8)	25.4 (3.2)	25.9 (3.5)
Smokers	26 (21.3%)	33 (26.6%)	59 (24.0%)	61 (21.0%)	120 (22.4%)
Family history of varicose veins	86 (70.5%)	91 (73.4%)	177 (72.0%)	206 (71.0%)	383 (71.5%)
Family history of leg ulceration	9 (7.4%)	20 (16.1%)	29 (11.8%)	50 (17.2%)	79 (14.7%)
Previous pregnancies (mean no.)	77 (2.1)	76 (2.1)	153 (2.1)	168 (1.7)	321 (1.9)

[a] $p < 0.05$, χ^2 test.

hospital, GP or other healthcare professionals regarding varicose veins or leg symptoms.

Amongst those randomised to surgical treatment, there were two major complications (1.6%). One patient developed a foot drop following a saphenopopliteal ligation. This was treated by physiotherapy for a period of 6 weeks, and he was seen on a total of four occasions in the first year in the outpatient department. The foot drop had completely resolved by 8 weeks after surgery. One patient developed cellulitis and was readmitted to hospital five days following surgery. She was treated by intravenous antibiotics and remained in hospital for 9 days.

Minor complications were reported by 20 patients (15.3%) and comprised pain (3), bleeding (2), postoperative hypotension (1), retained suture (1), allergy to bandages (1) and wound infections (12), of whom two reported wound discharge or persistent problems. Two other patients (1.6%) had additional visits to their GP regarding bruising.

In addition to those patients who reported symptoms or problems at the 1-year assessment, there were a further 14 (17.7%) who noted numbness on direct questioning, six (7.6%) who were concerned regarding their scars and three (3.8%) who reported some element of skin staining. None of these were volunteered as complications or problems in response to open questioning.

Of the 290 patients who declined randomisation, 198 underwent surgery in the first year, 85 were treated conservatively and seven underwent sclerotherapy. None of those patients treated conservatively reported complications or further contact with health professionals during the first year of treatment. There were no major complications; minor complications of all treatments were as listed in *Table 31*.

Symptoms

The symptoms reported at initial assessment are shown in *Table 32*. Overall, the most commonly reported symptoms were aching (84.1%), followed by cosmetic problems (69.6%), itching (58.8%), heaviness (55.2%) and swelling (44.4%). Relief of symptoms through the use of compression hosiery was reported in 31% of patients. There was a higher incidence of itching amongst those who declined randomisation (64.1% vs 52.4%, $p < 0.05$, χ^2 test) but no other significant difference between those who were randomised compared with those who declined randomisation, or between the arms of the RCT.

For all the reported symptoms there were significant differences in outcome with surgery resulting in greater symptomatic relief than conservative treatment (see *Table 33*). The differences at 2 years were not significant; however, this is based upon the ITT analysis and a significant proportion of the patients in the conservative arm had undergone surgical treatment by this time. The symptoms reported in those patients who declined randomisation are shown in *Table 34*.

Anatomical extent and progression

There was no significant difference in anatomical extent between the arms of the randomised trial but those who declined randomisation had significantly more extensive varicosities ($p < 0.05$, chi-squared test for trend).

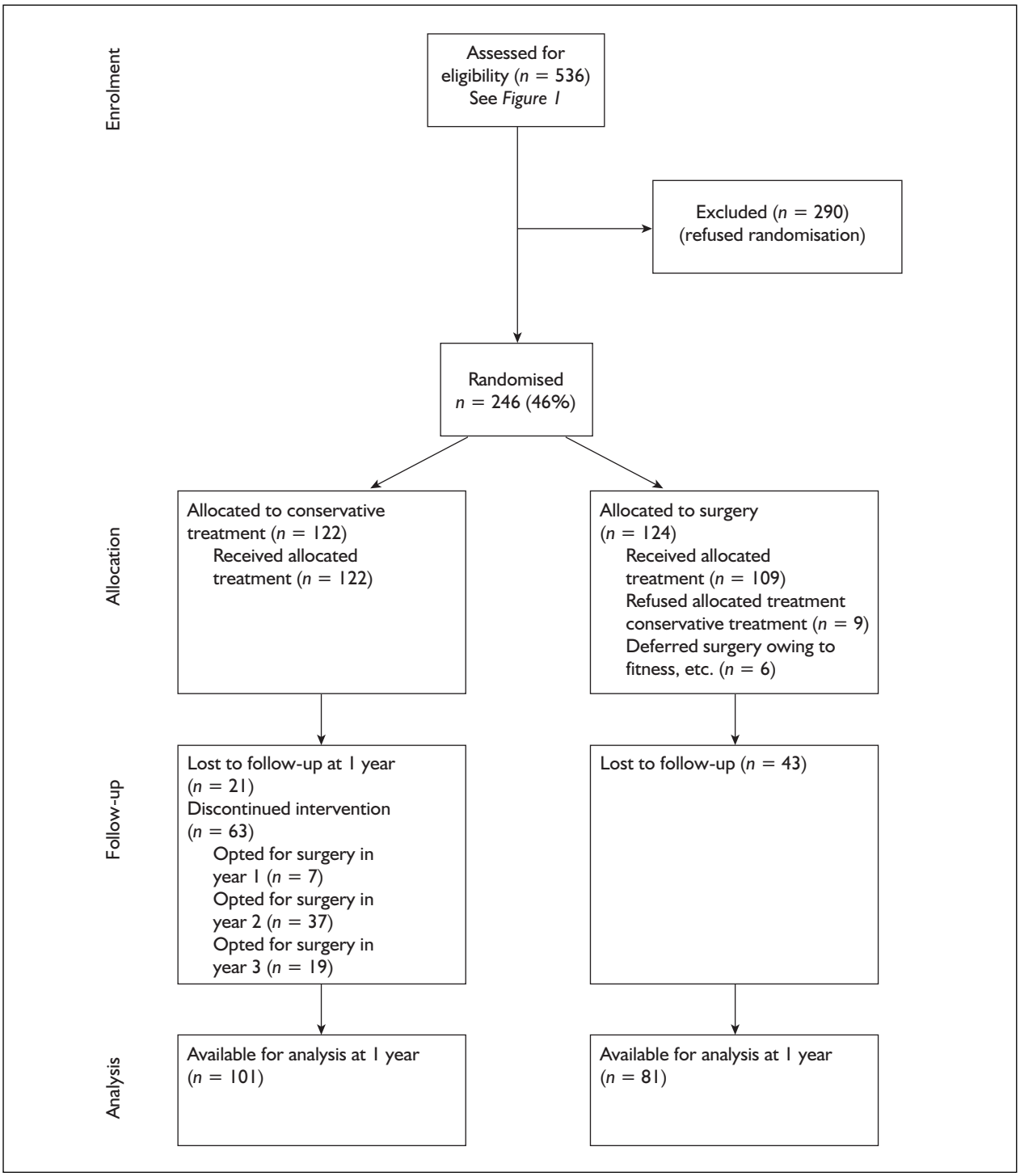

FIGURE 11 *Outcome for Group 3 patients*

Figure 12 shows the anatomical extent at baseline and at the 1-year follow-up in patients allocated to conservative treatment and surgery. There was no significant difference in the conservatively treated patients, whereas in those treated by surgery 70% had no varicose veins on clinical assessment at 1 year ($p < 0.05$, chi-squared test for trend).

The development of new varicose veins was reported in 11 of 172 patients (6.4%) at 1 year, and in 36 of 100 patients (36%) at 2 years. At 2 years there were more patients reporting new veins in the conservatively treated arm (40.7% versus 30.4%, not significant), but these are based on small numbers and a significant

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TABLE 31 *Summary of complications in Group 3*

Complication	No. (%)	Comments
Randomised to conservative treatment		
Skin problems	1 (0.3)	
Phlebitis in first year	3 (1.0)	
Swelling	1 (0.3)	
Randomised to surgery		
Foot drop	1 (0.8)	
Cellulitis	1 (0.8)	Required readmission to hospital
Leg pains	3 (2.4)	1 seen in hospital on one occasion
Overnight stay following planned day-case	2 (1.6)	1 for bleeding, 1 for hypotension
Wound infection	12 (9.6)	2 with recorded wound discharge
Retained suture	1 (0.8)	
Bleeding on bandage removal	1 (0.8)	
Allergy to bandage	1 (0.8)	
Non-randomised		
Wound infection	6	
Bleeding on bandage removal	1	
Tight bandage	1	
Haematoma	1	
Neuropraxia	1	
Staining after sclerotherapy	1	

TABLE 32 *Symptoms at initial assessment of Group 3 patients by result of randomisation*

	Randomised to conservative treatment	Randomised to surgery	All randomised patients	Declined randomisation	Total
N	122	124	246	290	536
Aching	97 (79.5%)	107 (86.3%)	204 (82.9%)	247 (85.2%)	451 (84.1%)
Heaviness	64 (52.5%)	74 (59.7%)	138 (56.1%)	158 (54.5%)	296 (55.2%)
Itching	69 (56.6%)	60 (48.4%)	129 (52.4%)	186 (64.1%)	315 (58.8%)
Swelling	47 (38.5%)	54 (43.5%)	101 (41.1%)	137 (47.2%)	238 (44.4%)
Cosmetic concerns	91 (74.6%)	90 (72.6%)	181 (73.6%)	192 (66.2%)	373 (69.6%)

TABLE 33 *Symptoms reported as better, the same or worse at 1-year assessment in randomised arms of Group 3 trial*

	Conservative				Surgery			
	None	Better	Same	Worse	None	Better	Same	Worse
Aching[a]	18 (19%)	7 (7%)	45 (46%)	27 (28%)	23 (31%)	37 (49%)	10 (13%)	5 (7%)
Heaviness[a]	42 (43%)	3 (3%)	31 (32%)	21 (22%)	39 (52%)	27 (36%)	6 (8%)	3 (4%)
Itching[a]	44 (45%)	11 (11%)	21 (22%)	21 (22%)	42 (56%)	23 (31%)	8 (11%)	2 (3%)
Swelling[a]	58 (60%)	8 (8%)	19 (20%)	12 (12%)	54 (72%)	13 (17%)	4 (5%)	4 (5%)
Cosmetic concerns[a]	21 (22%)	1 (1%)	44 (45%)	31 (32%)	15 (20%)	47 (63%)	7 (9%)	6 (8%)

[a] $p < 0.05$, χ^2 test for trend.

TABLE 34 *Symptoms reported as better, the same or worse at 1-year assessment in those who declined randomisation in Group 3 trial*

	None	Better	Same	Worse
Aching	109 (54%)	60 (30%)	22 (11%)	11 (5%)
Heaviness	139 (69%)	40 (20%)	18 (9%)	5 (2%)
Itching	136 (67%)	40 (20%)	19 (9%)	7 (3%)
Swelling	139 (69%)	34 (17%)	19 (9%)	10 (5%)
Cosmetic concerns	96 (48%)	69 (34%)	26 (13%)	11 (5%)

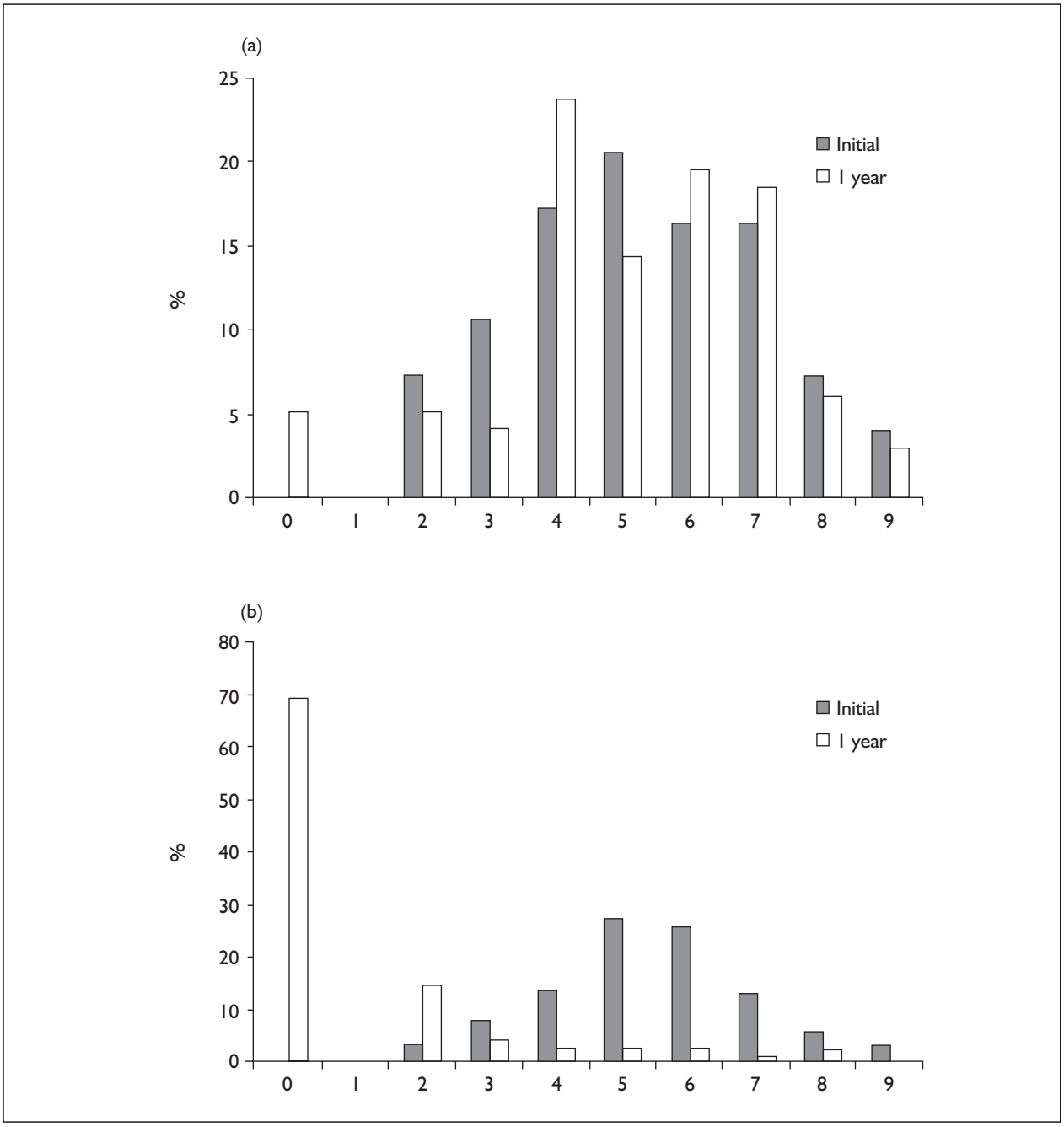

FIGURE 12 *Anatomical extent at baseline and 1 year assessment for patients in Group 3 randomised to (a) conservative treatment and (b) surgery: proportion (%) in each anatomical category as defined in* Table 7

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TABLE 35 *Quality of life outcomes for Group 3 Trial*

	Baseline		1 year		2 years	
	Conservative	**Surgery**	**Conservative**	**Surgery**	**Conservative**	**Surgery**
SF-6D	0.74 (0.11) *n* = 103	0.73 (0.10) *n* = 95	0.73 (0.11)* *n* = 98	0.77 (0.10)* *n* = 75	0.72 (0.13)* *n* = 47	0.78 (0.10)* *n* = 44
EQ-5D	0.77 (0.18) *n* = 102	0.76 (0.19) *n* = 98	0.78 (0.18)* *n* = 101	0.87 (0.14)* *n* = 78	0.85 (0.17) *n* = 44	0.84 (0.21) *n* = 34
VAS	0.77 (0.17) *n* = 101	0.78 (0.15) *n* = 98	0.75 (0.18)* *n* = 100	0.82 (0.13)* *n* = 77	0.75 (0.20)* *n* = 44	0.81 (0.14)* *n* = 34
SG	0.95 (0.11) *n* = 98	0.94 (0.11) *n* = 94	0.95 (0.14) *n* = 80	0.95 (0.15) *n* = 65		

Values in parentheses are the standard deviation.
* Significant difference ($p < 0.05$) for conservative treatment vs surgery.
SG, standard gamble.

proportion of patients in the conservatively treated group had undergone surgery by this time.

Quality of life

Summary results for the HRQoL measures are shown in *Table 35*. Based on the primary end-point of the SF-6D index, the utility in those randomised to surgery was significantly higher than those randomised to conservative treatment at 1 year (0.77 versus 0.73) and 2 years (0.78 versus 0.72, $p < 0.05$, paired *t*-test). Similar differences were present in the EQ-5D and VAS at 12 months. More detailed analysis of the HRQoL data is provided in Chapter 5.

Patient satisfaction

At the 1-year follow-up, three of 65 patients (4.6%) undergoing surgical treatment and 53 of 107 (49.5%) treated conservatively expressed dissatisfaction with their initial treatment ($p < 0.05$, χ^2 test).

Key points

- Group 3 patients formed the largest cohort, with 536 patients being identified as suitable, of whom 246 consented to randomisation.
- Compared with the other groups, there was a higher proportion of males (33%) and the average age was older (50.4%).
- Of those randomised to conservative treatment, many were dissatisfied and, by the end of the third year of follow-up, over half (51.6%) had chosen to withdraw from conservative treatment and undergo surgery
- Of those patients randomised to surgery, there were two major complications (one foot drop and one cellulitis, requiring hospitalisation).
- The surgical arm of the trial showed better results for symptoms, anatomical extent, HRQoL and patient satisfaction at 1-year follow-up.

Overall results of treatment

As some of the arms in the RCTs included only small numbers of patients for follow-up, further data were analysed on the basis of initial treatment carried out in order to obtain estimates of outcomes and complication rates for each of the treatments and to inform the sensitivity analysis used in the modelling (Chapter 6). This section combines the results for all patients undergoing each modality of treatment, whether as part of one of the RCTs or as a chosen treatment.

Overall, of the 1009 patients recruited to the randomised and observational arms of the trials, the initial treatment was conservative in 387 patients, sclerotherapy in 91 and surgery in 531. *Table 36* provides details of the demographics of these patients, based on initial treatment. Those undergoing sclerotherapy included a greater proportion of females, were younger and had lower BMI than those undergoing conservative treatment, with patients receiving surgery being intermediate in all these respects.

Of the 1009 patients recruited, 391 (38.8%) had some varicose veins present in the second leg. This was more common with increasing severity (Group 1, 23.4%; Group 2, 28.4%; and Group 3, 40.5%, $p < 0.05$, χ^2 test for trend). Of those for whom information was available for at least the

TABLE 36 *Demographics and clinical features of all patients by initial treatment*

	Conservative	Sclerotherapy	Surgery	Total
N	387	91	531	1009
Sheffield:Exeter	262:125	46:45	160:371	468:541
Female:male	260:127	79:12	388:143	727:282
Age (SD) (years)	51.5 (14.4)	47.2 (13.1)	49.4 (12.7)	50.0 (13.5)
Height (SD) (cm)	167.8 (9.8)	165.3 (8.2)	167.8 (9.7)	167.6 (9.6)
BMI (SD)	27.6 (4.9)	25.5 (4.2)	26.4 (4.4)	26.8 (4.6)
Smokers	87 (22.5%)	23 (25.3%)	110 (20.7%)	220 (21.8%)
Family history of varicose veins	265 (68.5%)	65 (71.4%)	388 (73.1%)	718 (71.2%)
Family history of leg ulceration	45 (11.6%)	7 (7.7%)	105 (19.8%)	157 (15.6%)
Previous pregnancies (mean no.)	226 (2.0)	67 (2.1)	346 (1.9)	639 (2.0)

TABLE 37 *Summary of all complications of surgery (531 cases)*

Complication	Total	Major	Comments
Chest infection	1 (0.2%)	1 (0.2%)	Readmitted to hospital for 7 days
Bleeding	3 (0.6%)	(0.0%)	Minor, no transfusions, 1 stayed overnight following planned day-case procedure
Allergy bandage or skin preparation	4 (0.8%)	(0.0%)	
Phlebitis	2 (0.4%)	(0.0%)	
Haematoma	3 (0.6%)	(0.0%)	None requiring intervention
Wound infection	28 (5.3%)	3 (0.6%)	7 with wound discharge, 1 readmitted for drainage
Cellulitis	2 (0.4%)	1 (0.2%)	1 readmitted for antibiotics
DVT	3 (0.6%)	3 (0.6%)	See text
Foot drop	2 (0.4%)	1 (0.2%)	1 definite, 1 possible, both resolved completely
Urinary retention	1 (0.2%)	(0.0%)	1-night stay following planned day-case procedure
Retained suture	2 (0.4%)	(0.0%)	
Hypotension	1 (0.2%)	(0.0%)	1-night stay following planned day-case procedure
Pain	6 (1.1%)	(0.0%)	
Staining/scarring	7 (1.3%)	(0.0%)	
Total	65 (12.2%)	9 (1.7%)	

first year, 129 of 471 patients (27.4%) underwent bilateral surgery, with 31 of these (24.0%) being carried out as staged unilateral procedures. Of those who initially underwent unilateral surgery, three (0.9%) underwent a second procedure on the other leg within the 3-year follow-up period.

Complications

In those patients who were treated conservatively, 12 (3.1%) reported episodes of phlebitis within the first year following initial assessment. A further patient developed a haematoma and seven other patients had visited their GP for other reasons relating to the veins, including leg swelling and discomfort.

Of those who underwent sclerotherapy, 13 patients reported complications (14.3%), the complications reported being phlebitis (3), pain (1), blistering at the site of injections (4) and pigmentation (5). A further 20 patients reported skin staining on direct questioning at 1-year assessment, giving a total rate of skin staining of 43.1% on those assessed at 1 year, although of these 19 of the 25 (76%) stated that overall they were satisfied with the results of treatment.

For those patients who underwent surgery, the complications are summarised in *Table 37*. Some of the individual complications have been described in the RCTs above. The additional major complications were two cases of DVT, a 52-year-old patients with a personal and family history of DVT in whom a diagnosis of anti-phospholipid syndrome was made and a 42-year-old women who developed palpitations for which she was

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TABLE 38 *Symptoms at initial assessment of all patients by initial treatment*

	Conservative	Sclerotherapy	Surgery	Total
N	387	91	531	1009
Aching	306 (79.1%)	85 (93.4%)	480 (90.4%)	871 (86.3%)
Heaviness	191 (49.4%)	53 (58.2%)	339 (63.8%)	583 (57.8%)
Itching	203 (52.5%)	48 (52.7%)	338 (63.7%)	589 (58.4%)
Swelling	157 (40.6%)	45 (49.5%)	277 (52.2%)	479 (47.5%)
Cosmetic concerns	252 (65.1%)	59 (64.8%)	382 (71.9%)	693 (68.7%)

TABLE 39 *Symptoms at 1 year in all patients, by initial treatment*

Symptom	Treatment	None	Better	Same	Worse
Aching	Conservative	57 (21.8%)	99 (37.8%)	45 (17.2%)	61 (23.3%)
	Sclerotherapy	20 (32.3%)	17 (27.4%)	21 (33.9%)	4 (6.5%)
	Surgery	159 (45.8%)	28 (8.1%)	148 (42.7%)	12 (3.5%)
Heaviness	Conservative	126 (48.1%)	75 (28.6%)	24 (9.2%)	37 (14.1%)
	Sclerotherapy	36 (58.1%)	14 (22.6%)	12 (19.4%)	(0.0%)
	Surgery	206 (59.4%)	21 (6.1%)	111 (32.0%)	9 (2.6%)
Itching	Conservative	133 (50.8%)	62 (23.7%)	23 (8.8%)	44 (16.8%)
	Sclerotherapy	38 (61.3%)	8 (12.9%)	14 (22.6%)	2 (3.2%)
	Surgery	223 (64.3%)	16 (4.6%)	101 (29.1%)	7 (2.0%)
Swelling	Conservative	155 (59.2%)	61 (23.3%)	20 (7.6%)	26 (9.9%)
	Sclerotherapy	42 (67.7%)	12 (19.4%)	5 (8.1%)	3 (4.8%)
	Surgery	227 (65.4%)	22 (6.3%)	86 (24.8%)	12 (3.5%)
Cosmetic concerns	Conservative	64 (24.4%)	115 (43.9%)	10 (3.8%)	73 (27.9%)
	Sclerotherapy	22 (35.5%)	14 (22.6%)	22 (35.5%)	4 (6.5%)
	Surgery	129 (37.2%)	21 (6.1%)	182 (52.4%)	15 (4.3%)

investigated by cardiologists and found to have atrial flutter. One other patient complained of numbness and weakness in the foot following a saphenopopliteal ligation. She was not referred back to hospital and when seen for routine follow-up there was some residual numbness but no weakness.

Overall, wound infection or cellulitis was reported by 30 patients (5.6%), with the majority (17) requiring only a single visit to their GP. Seven patients reported wound discharge and two were readmitted to hospital, one with an abscess requiring drainage.

Symptoms

Table 38 gives the symptoms that were reported at recruitment and *Table 39* shows the change in symptoms at one year. For all symptoms, surgery and sclerotherapy resulted in a lower rate of reported symptoms at 1 year compared with conservative treatment.

Anatomical extent and progression

The anatomical extent of varicose veins at baseline and 1 year is illustrated in *Figure 13*. As might be expected from the indications, patients undergoing sclerotherapy had the least extensive veins at initial assessment. The 1-year follow-up showed no significant change in the extent of varicose veins in those treated conservatively, whereas those treated by surgery had the greatest proportion in whom no veins were present on clinical assessment (*Figure 14*).

The development of new varicose veins was reported by 10.9% of patients in the first year. At 2 years, new varicose veins were reported by 43.3% of all those completing questionnaires with 7.4% reporting ‘a lot’ of new veins.

Quality of life

Summary results of the HRQoL outcomes are shown in *Table 40*. At the baseline assessment, there was no significant difference, but a trend

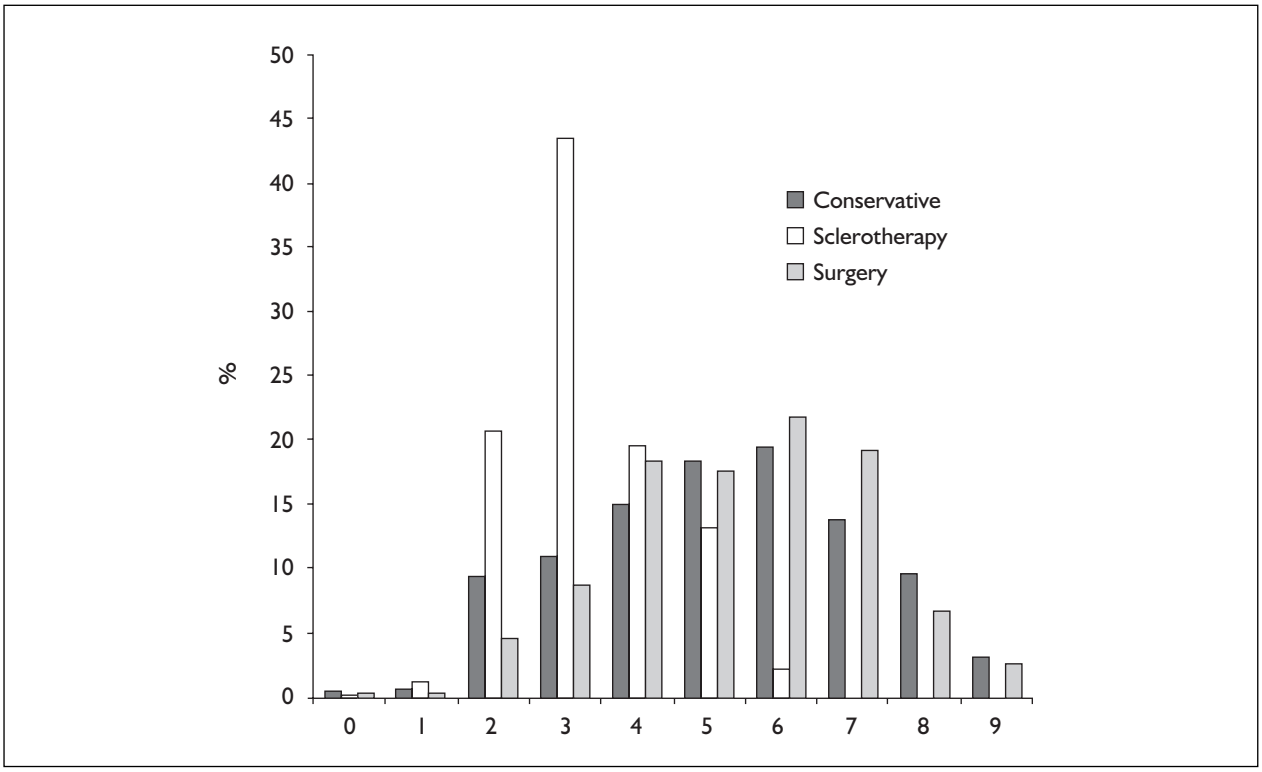

FIGURE 13 *Initial anatomical extent in patients by initial treatment: proportion (%) in each anatomical category as defined in* Table 7

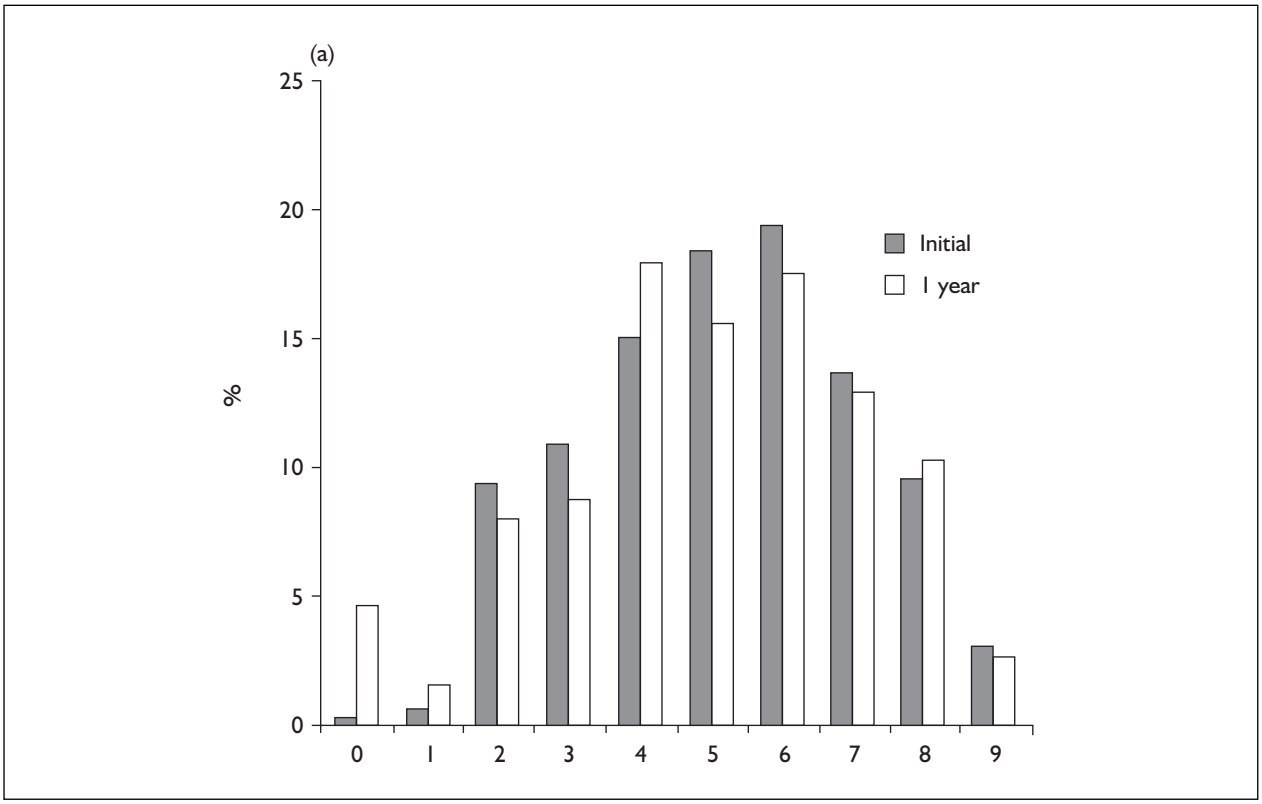

FIGURE 14 *Anatomical extent at baseline and 1-year assessment for all patients undergoing (a) conservative treatment, (b) sclerotherapy and (c) surgery: proportion (%) in each anatomical category as defined in* Table 7

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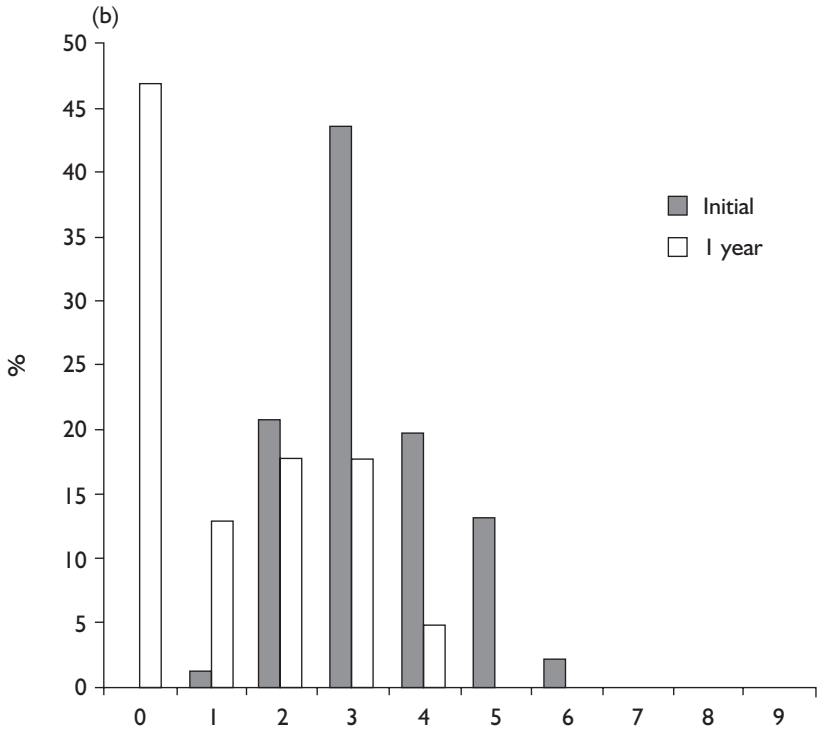

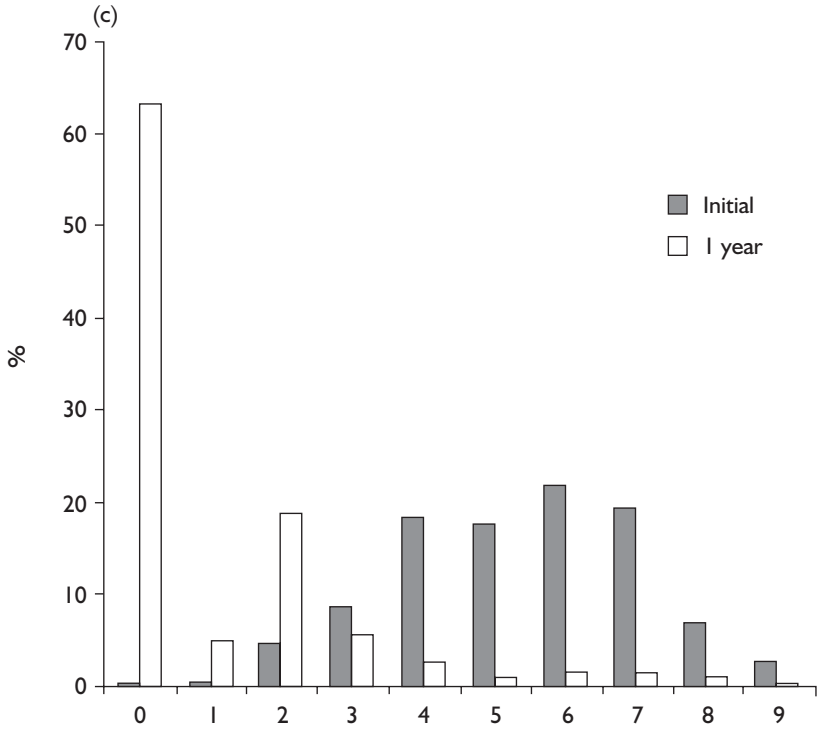

FIGURE 14 *(cont'd) Anatomical extent at baseline and 1-year assessment for all patients undergoing (a) conservative treatment, (b) sclerotherapy and (c) surgery: proportion (%) in each anatomical category as defined in* Table 7

TABLE 40 *Quality of life outcomes for all treatments*

	Conservative	Sclerotherapy	Surgery
Baseline			
SF-6D	0.72 (0.11), *n* = 312	0.69 (0.10), *n* = 81	0.72 (0.10), *n* = 492
EQ-5D	0.77 (0.18), *n* = 316	0.73 (0.19), *n* = 83	0.75 (0.17), *n* = 488
VAS	0.76 (0.17), *n* = 315	0.75 (0.17), *n* = 84	0.77 (0.15), *n* = 489
SG	0.95 (0.11), *n* = 288	0.93 (0.12), *n* = 74	0.94 (0.11), *n* = 466
1 year			
SF-6D	0.72 (0.12), *n* = 261	0.72 (0.12), *n* = 64	0.76 (0.10), *n* = 365
EQ-5D	0.77 (0.21), *n* = 265	0.80 (0.22), *n* = 63	0.85 (0.17), *n* = 369
VAS	0.75 (0.18), *n* = 263	0.77 (0.19), *n* = 62	0.82 (0.14), *n* = 368
SG	0.95 (0.13), *n* = 28	0.98 (0.08), *n* = 60	0.94 (0.22), *n* = 362
2 years			
SF-6D	0.70 (0.12), *n* = 168	0.73 (0.12), *n* = 37	0.76 (0.11), *n* = 185
EQ-5D	0.80 (0.19), *n* = 153	0.81 (0.15), *n* = 30	0.86 (0.17), *n* = 166
VAS	0.74 (0.19), *n* = 156	0.77 (0.17), *n* = 32	0.83 (0.13), *n* = 166

Values in parentheses are the standard deviation.
[d] SG, standard gamble.

towards lower average HRQoL on the EQ-5D and SF-6D scales in the sclerotherapy group. At 1 and 2 years, those treated by surgery had a significantly higher HRQoL compared with both of the other groups. More detailed analysis of the HRQoL data is provided in Chapter 5.

Patient satisfaction

At 1-year follow-up, 26 of 348 (7.5%) patients who underwent surgery were dissatisfied with the result, compared with 13 of 62 (21.0%) patients who underwent sclerotherapy and 78 of 261 (29.9%) patients who underwent conservative treatment.

Key points

- A total of 531 patients underwent surgery, 91 sclerotherapy and 387 were treated conservatively.
- Following sclerotherapy there were no serious complications but 14.3% reported minor complications, which included phlebitis, blistering at the injection site, and skin staining. The proportion reporting skin staining at one year on direct questioning was 43.1%.
- Following surgery, there were nine major complications (1.7%) including DVT (3), foot drop (1) and serious infection requiring readmission to hospital (5).
- Following surgery, self-reported wound infection rates were 5.6%.
- The observational data were similar to those reported in the RCTs, with surgical treatment providing the best results in terms of symptom relief, improvement in anatomical extent of varicose veins, HRQoL and patient satisfaction.

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Chapter 5
Economic analysis

Introduction

This chapter deals with the economic analysis that was carried out alongside the randomised controlled trials. The first part deals with the methods and results of cost and effectiveness data collection from the randomised patients in each of the RCTs, followed by cost-effectiveness analysis. The subsequent part describes a WTP exercise, which was carried out using a separate cohort of patients with varicose veins, in order to assess the strength of patient preferences for the treatment options.

Methods

The economic analysis was designed as a cost-effectiveness study with the main outcome measure being the SF-6D. The EQ-5D was used as a secondary outcome measure. There were three main groups of patients within the clinical trial who received treatment according to the severity of their condition. Patients in Group 1 were diagnosed with mild BK varicose veins and were randomised to receive either conservative treatment or sclerotherapy. The main symptoms for patients in Group 1 related to cosmetic appearance and aching, and there was no evidence of reflux or complications. Patients in Group 2 were diagnosed with moderate BK varicose veins associated with evidence of saphenofemoral or saphenopopliteal reflux and were randomised to receive either sclerotherapy or surgery. Patients in Group 3 were diagnosed with extensive BK or AK varicosities with evidence of saphenofemoral or saphenopopliteal reflux. These patients were randomised to receive conservative treatment or surgical intervention. Incremental cost-effectiveness ratios (ICERs) were estimated for each group. An NHS perspective was adopted for the estimation of costs with all secondary and primary care treatment costs included.

Costs

NHS treatment costs included all NHS contacts with primary and secondary healthcare services and treatments and medications administered. Details of healthcare utilisation were collected from two main sources, GP notes and the clinical trial resource use database. GP notes were examined for all patients to collect information on the number and type of GP and practice nurse contacts and any treatment(s) prescribed. Other healthcare usage over the 3-year period was collected by means of the clinical trial resource use database administered by the research nurses responsible for clinical trial coordination at each of the two sites. Information was collected on hospitalisations, outpatient visits, contacts with other healthcare professionals, treatments for varicose veins and any treatments for complications.

Unit costs for all resources used by trial patients were obtained for the financial year 2002–3 and were obtained using national sources wherever possible, including the Personal Social Services Research Unit Database,[185] NHS Reference Costs[186] and the BNF.[187] Where national costs were unavailable, local unit costs were obtained from the finance departments at each of the two participating hospitals.

Health outcome measures

The SF-6D and EQ-5D were used to assess HRQoL. Patients in the trial were surveyed (using a self-completion questionnaire containing both of these instruments) at baseline, and at 1, 6, 12, 24 and 36 months. The responses to the EQ-5D were converted into utility scores using the tariff of values generated from the York MVH project.[181] The SF-36 was transformed into the SF-6D, a single preference-based measure of health using the algorithm derived by Brazier and colleagues.[188] The utilities generated from each measurement instrument were plotted against time, and the area under the curve was calculated in order to measure the quality-adjusted life-year (QALY) gain for each patient.

Statistical techniques

All economic analyses were carried out on an ITT basis. Resource use, costs and health outcomes data were analysed using SPSS version 12.0. Despite the potential skewness of cost data, the arithmetic mean and standard *t*-test-based CIs are considered appropriate for comparing mean costs between two groups and the most relevant

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TABLE 41 *Comparison of mean resource use for Group 1 over 0–24 months*

Type of care	Conservative: mean (SD) *n* = 18	Sclerotherapy: mean (SD) *n* = 16
Retreatment	*n* = 4	–
Hospital inpatient admissions	–	–
Hospital outpatient visits	–	–
Accident and emergency visits	–	–
Anticoagulation clinic visits	–	–
GP visits	–	0.188 (0.544)
Visits to other healthcare professionals	–	–

TABLE 42 *Mean NHS costs of healthcare resource use for treatment for varicose veins, 0–24 months – Group 1*

Type of care	Conservative: mean (SD) (£) *n* = 18	Sclerotherapy: mean (SD) (£) *n* = 16
Initial treatment[a]	8.00 (0.00)	131.50 (61.27)
Retreatment[a]	35.56 (68.45)	–
Hospital admissions/visits	–	–
GP visits	–	2.00 (5.47)
Visits to other healthcare professionals	–	–
Total NHS costs[a] (undiscounted)	52.44 (73.74)	132.50 (62.50)
Total NHS costs (discounted)[a]	51.54 (72.26)	132.47 (62.47)

[a] Significant difference between the groups at the 5% level.

statistics for informing decision-making.[189] The validity of the results was confirmed using bootstrapping where the original data were used to provide an empirical estimate of the sampling distribution through repeated resampling from the observed data.[190] Owing to very high attrition rates at 36 months, the primary analysis reflected a comparison of costs to the NHS and QALYs measured using the SF-6D up to 24 months. Where SF-6D data were missing owing to individuals failing to respond to the questionnaire, values were imputed based on straight-line interpolation. Both costs and outcomes occurring during the 12–24-month period were discounted at 3.5%, the current recommended rate for public sector projects.[184]

Results

Group 1 trial

Costs

Table 41 shows the resources used by Group 1 during the 0–24-month period (excluding the resource use items associated with the initial treatment). There were no statistically significant differences in resource use between those patients randomised to receive conservative treatment or sclerotherapy. Four patients who were randomised to receive conservative treatment received retreatment in the form of sclerotherapy during the 24-month period and no patients who were randomised to receive sclerotherapy received retreatment.

Table 42 documents the mean NHS costs for Group 1 during the first 24 months of the trial. It can be seen that there were statistically significant differences in the costs of the initial treatment received, retreatment and in total NHS costs. The mean total (discounted) cost for those patients receiving scelerotherapy was £133.47 and the mean total (discounted) cost for those patients receiving conservative treatment was £51.54.

Health outcomes: SF-6D

The results from the base-case analysis of the SF-6D for Group 1 are presented in *Table 43*. It can be seen that there is a deterioration in HRQoL between 0 and 1 month for both treatment groups (although the reduction is more marked in the sclerotherapy-treated group) followed by a

TABLE 43 *Group 1 SF-36 scores translated into SF-6D (original data)*

	Conservative: mean (SD)	Sclerotherapy: mean (SD)	Difference in means	95% CI
Baseline	0.728 (0.086) $n = 17$	0.714 (0.112) $n = 15$	0.014	–0.058 to 0.086
1 month	0.643 (0.076) $n = 12$	0.569 (0.074) $n = 13$	0.074	–0.009 to 0.157
6 months	0.670 (0.112) $n = 10$	0.702 (0.148) $n = 8$	–0.032	–0.161 to 0.100
12 months	0.739 (0.074) $n = 15$	0.724 (0.161) $n = 13$	0.014	–0.080 to 0.110
24 months	0.706 (0.116) $n = 6$	0.669 (0.158) $n = 5$	0.037	–0.151 to 0.224
Area under curve from 0 to 12 months	0.680 (0.092) $n = 9$	0.640 (0.124) $n = 6$	0.040	–0.080 to 0.160
Area under curve from 0 to 24 months (discounted)	1.358 (0.193) $n = 6$	1.353 (0.307) $n = 3$	0.005	–0.382 to 0.392

considerable improvement in health status from 6 to 12 months for both treatment groups. Over this period, the improvement in health status for the sclerotherapy-treated group is slightly higher than that for the conservative group but the difference is not statistically significant. Over the 12–24-month period, the health status of both treatment groups falls slightly. The QALY gain over the 24-month period for the conservatively treated group is slightly higher than for the sclerotherapy-treated group, although the very small numbers of individuals in each treatment group at 24 months mean that these results should be interpreted with considerable caution. Where missing values are imputed based on straight-line interpolation (*Table 44*), the fall in health status over the 12–24-month period is less pronounced than in the base-case analysis and the QALY gain results are reversed in that the QALY gain for the sclerotherapy treated group is slightly higher than that for the conservatively treated group.

Health outcomes: EQ-5D

The results from the analysis of the EQ-5D for Group 1 are presented in *Tables 45* and *46*. As with the SF-6D results, the very small numbers of individuals in each treatment group mean that the results should be interpreted with caution. In contrast to the SF-6D results, the base-case EQ-5D results (*Table 45*) indicate an improvement in health status for both treatment groups between 0 and 1 month and a slight deterioration between 1 and 6 month. There is a sustained improvement in health status from 12 to 24 months for both treatment groups. The difference in health status between 12 and 24 months is largely due to a proportion of patients ($n = 3$) who reported themselves in perfect health at 24 months according to the EQ-5D classification, whereas no patients were classified in perfect health according to the SF-6D. Where missing data are imputed (*Table 46*), the results are broadly similar to the base-case analysis in that the QALY gain at 24 months is slightly higher for the sclerotherapy group, although there is a slight fall in health status between 12 and 24 months for this. However, the very small numbers of individuals in each treatment group mean that the results should be interpreted with caution.

Cost-effectiveness analysis

Unfortunately, the number of patients in Group 1 was too small to undertake meaningful cost-effectiveness analysis. This issue is considered by the economic model in Chapter 6.

Group 2 trial

Costs

Table 47 shows the resources used by Group 2 during the 0–24-month period (excluding the resource use items associated with the initial treatment). There were no statistically significant differences in resource use between those patients randomised to receive sclerotherapy or surgery. Three patients who were randomised to receive sclerotherapy received retreatment in the form of

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TABLE 44 *Group 1 SF-36 scores translated into SF-6D (imputed data for missing values)*

	Conservative: mean (SD)	Sclerotherapy: mean (SD)	Difference in means	95% CI
Baseline	0.728 (0.086) *n* = 17	0.714 (0.112) *n* = 15	0.014	–0.058 to 0.086
1 month	0.667 (0.086) *n* = 17	0.587 (0.132) *n* = 15	0.080	–0.001 to 0.161
6 months	0.696 (0.095) *n* = 16	0.685 (0.135) *n* = 13	0.011	–0.077 to 0.010
12 months	0.739 (0.074) *n* = 15	0.724 (0.161) *n* = 13	0.015	–0.080 to 0.110
24 months	0.706 (0.116) *n* = 6	0.678 (0.144) *n* = 8	0.028	–0.128 to 0.185
Area under curve from 0 to 12 months	0.700 (0.080) *n* = 14	0.669 (0.133) *n* = 12	–0.005	–0.095 to 0.085
Area under curve from 0 to 24 months (discounted)	1.358 (0.193) *n* = 6	1.347 (0.233) *n* = 7	0.111	–0.253 to 0.275

TABLE 45 *Group 1 EQ-5D scores (original data)*

	Conservative: mean (SD)	Sclerotherapy: mean (SD)	Difference in means	95% CI
Baseline	0.763 (0.185) *n* = 18	0.772 (0.133) *n* = 16	–0.008	–0.122 to 0.105
1 month	0.828 (0.151) *n* = 12	0.868 (0.130) *n* = 13	–0.040	–0.156 to 0.076
6 months	0.731 (0.282) *n* = 10	0.766 (0.301) *n* = 36	–0.035	–0.327 to 0.257
12 months	0.724 (0.284) *n* = 15	0.821 (0.268) *n* = 12	–0.097	–0.319 to 0.124
24 months	0.808 (0.110) *n* = 5	0.839 (0.172) *n* = 5	0.031	–0.241 to 0.180
Area under curve from 0 to 12 months	0.760 (0.251) *n* = 9	0.788 (0.266) *n* = 6	–0.028	–0.321 to 0.264
Area under curve from 0 to 24 months (discounted)	1.594 (0.172) *n* = 5	1.707 (0.424) *n* = 3	–0.113	–0.618 to 0.392

surgery (n = 2) and repeat sclerotherapy (n = 1). In addition, one patient who was randomised to receive surgery received repeat surgery.

Table 48 documents the mean NHS costs for Group 2 during the first 24 months of the trial. It can be seen that there were statistically significant differences in the costs of the initial treatment received and in total NHS costs. The mean total (discounted) cost for those patients receiving surgery was £701.28 and the mean total (discounted) cost for those patients receiving sclerotherapy was £210.94.

Health outcomes: SF-6D

For Group 2, the results of the analysis of the SF-6D are broadly similar to those of Group 1 (*Table 49*) in that there is a deterioration in HRQoL between 0 and 1 month for both treatment groups (although the reduction is more marked in the surgically treated group) followed by a considerable improvement in health status

TABLE 46 *Group 1 EQ-5D scores (imputed data for missing values)*

	Conservative: mean (SD)	Sclerotherapy: mean (SD)	Difference in means	95% CI
Baseline	0.763 (0.185) *n* = 18	0.772 (0.133) *n* = 16	–0.008	–0.122 to 0.105
1 month	0.802 (0.137) *n* = 17	0.865 (0.125) *n* = 14	–0.063	–0.161 to 0.034
6 months	0.739 (0.244) *n* = 16	0.819 (0.243) *n* = 13	–0.080	–0.266 to 0.107
12 months	0.724 (0.284) *n* = 15	0.798 (0.269) *n* = 13	–0.075	–0.291 to 0.142
24 months	0.808 (0.110) *n* = 5	0.761 (0.200) *n* = 8	0.047	–0.170 to 0.263
Area under curve from 0 to 12 months	0.753 (0.213) *n* = 17	0.918 (0.306) *n* = 12	–0.165	–0.362 to 0.033
Area under curve from 0 to 24 months (discounted)[a]	1.517 (0.253) *n* = 7	1.789 (0.399) *n* = 7	–0.271	–0.661 to 0.118

[a] Significant difference in means at the 5% level.

TABLE 47 *Comparison of mean resource use for Group 2 over 0–24 months*

Type of care	Sclerotherapy: mean (SD) *n* = 41	Surgery: mean (SD) *n* = 36
Retreatment	*n* = 3	*n* = 1
Hospital inpatient admissions	–	0.028 (0.167)
Hospital outpatient visits	–	–
Accident and emergency visits	–	0.028 (0.167)
Anticoagulation clinic visits	–	–
GP visits	0.098 (0.300)	0.139 (0.424)
Visits to other healthcare professionals	–	0.056 (0.232)

TABLE 48 *Mean NHS costs of healthcare resource use for treatment for varicose veins, 0–24 months – Group 2*

Type of care	Sclerotherapy: mean (SD) *n* = 41	Surgery: mean (SD) *n* = 36
Initial treatment[a]	187.80 (124.31)	669.83 (202.38)
Retreatment	39.51 (160.26)	20.28 (121.67)
Hospital admissions/visits	–	9.39 (46.47)
GP visits	1.56 (4.81)	1.78 (5.10)
Visits to other healthcare professionals	–	0.89 (3.72)
Total NHS costs (undiscounted)[a]	228.88 (199.31)	701.28 (176.69)
Total NHS costs (discounted)[a]	210.94 (167.29)	701.25 (176.68)

[a] Significant difference between groups at the 5% level.

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TABLE 49 *Group 2 SF-36 scores translated into SF-6D (original data)*

	Sclerotherapy: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.690 (0.099) *n* = 34	0.715 (0.095) *n* = 31	0.025	–0.073 to 0.023
1 month	0.587 (0.119) *n* = 22	0.578 (0.113) *n* = 22	0.009	–0.062 to 0.080
6 months	0.722 (0.120) *n* = 19	0.719 (0.109) *n* = 13	0.003	–0.082 to 0.088
12 months	0.717 (0.112) *n* = 28	0.764 (0.099) *n* = 24	–0.052	–0.112 to 0.007
24 months	0.747 (0.114) *n* = 15	0.761 (0.108) *n* = 16	–0.014	–0.096 to 0.067
Area under curve from 0 to 12 months	0.673 (0.115) *n* = 11	0.701 (0.071) *n* = 7	–0.029	–0.132 to 0.074
Area under curve from 0 to 24 months (discounted)	1.452 (0.259) *n* = 7	1.414 (0.152) *n* = 4	0.045	–0.280 to 0.370

TABLE 50 *Group 2 SF-36 scores translated into SF-6D (imputed data for missing values)*

	Sclerotherapy: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.699 (0.099) *n* = 34	0.715 (0.095) *n* = 31	–0.025	–0.073 to 0.023
1 month	0.609 (0.120) *n* = 30	0.612 (0.122) *n* = 29	–0.002	–0.065 to 0.061
6 months	0.699 (0.121) *n* = 29	0.717 (0.096) *n* = 26	–0.018	–0.078 to 0.042
12 months	0.713 (0.110) *n* = 29	0.768 (0.098) *n* = 26	–0.055	–0.112 to 0.002
24 months	0.726 (0.124) *n* = 18	0.752 (0.104) *n* = 19	–0.027	–0.103 to 0.049
Area under curve from 0 to 12 months	0.677 (0.108) *n* = 26	0.710 (0.077) *n* = 24	–0.034	–0.087 to 0.020
Area under curve from 0 to 24 months (discounted)	1.421 (0.219) *n* = 17	1.451 (0.150) *n* = 16	–0.031	–0.165 to 0.103

from 6 to 12 months for both treatment groups. Over the 12–24-month period, the health status of the surgically treated group falls slightly, whereas the health status of patients receiving sclerotherapy continues to improve on average. At 24 months, the QALY gain for the sclerotherapy group is higher than that for the surgically treated group. None of the differences in SF-6D scores between treatment groups at any time point are statistically significant, although this result is unsurprising given the small numbers of patients. Where missing values are imputed (*Table 50*), the results are broadly similar to the base-case analysis although the QALY gain for the surgically treated group is slightly higher than that for the sclerotherapy group.

Health outcomes: EQ-5D

The results from the analysis of the EQ-5D for Group 2 are presented in *Tables 51* and *52*.

TABLE 51 *Group 2 EQ-5D scores (original data)*

	Sclerotherapy: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.713 (0.206) *n* = 34	0.792 (0.143) *n* = 30	–0.079	–0.169 to 0.010
1 month	0.810 (0.264) *n* = 22	0.794 (0.243) *n* = 22	0.016	–0.138 to 0.170
6 months[a]	0.769 (0.171) *n* = 19	0.722 (0.312) *n* = 12	0.047	–0.130 to 0.224
12 months[a]	0.802 (0.144) *n* = 23	0.848 (0.201) *n* = 22	–0.046	–0.144 to 0.052
24 months	0.743 (0.112) *n* = 6	0.836 (0.315) *n* = 10	0.092	–0.381 to 0.197
Area under curve from 0 to 12 months	0.821 (0.167) *n* = 10	0.710 (0.295) *n* = 7	0.111	–0.128 to 0.350
Area under curve from 0 to 24 months (discounted)	1.332 (0.271) *n* = 3	1.810 (0.190) *n* = 4	–0.477	–0.920 to 0.033

[a] Significant difference in means at the 5% level.

TABLE 52 *Group 2 EQ-5D scores (imputed data for missing values)*

	Sclerotherapy: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.713 (0.206) *n* = 34	0.792 (0.143) *n* = 30	0.079	–0.169 to 0.010
1 month	0.754 (0.276) *n* = 30	0.786 (0.247) *n* = 23	–0.033	–0.164 to 0.099
6 months	0.744 (0.197) *n* = 30	0.790 (0.247) *n* = 23	–0.041	–0.163 to 0.084
12 months	0.803 (0.141) *n* = 29	0.828 (0.218) *n* = 23	–0.025	–0.126 to 0.075
24 months	0.793 (0.143) *n* = 14	0.819 (0.277) *n* = 14	–0.027	–0.198 to 0.144
Area under curve from 0 to 12 months	0.789 (0.161) *n* = 25	0.791 (0.211) *n* = 21	–0.002	–0.112 to 0.109
Area under curve from 0 to 24 months (discounted)[a]	1.584 (0.294) *n* = 14	1.612 (0.438) *n* = 13	–0.028	–0.321 to 0.265

[a] Significant difference in means at the 5% level.

In broad terms, the EQ-5D base-case results (*Table 51*) mirror those of the SF-6D in that there is a slight deterioration in HRQoL between 0 and 1 month followed by an improvement in the longer term. There are statistically significant differences between EQ-5D scores at the 6- and 12-month time points with the sclerotherapy group reporting higher EQ-5D scores on average at 6 months and the surgery group reporting higher EQ-5D scores on average at 12 months. The greater improvement for the surgery group is sustained over the 12–24-month period, although the differences at 24 months are not statistically significant. The QALY gain at 24 months is higher for the surgically treated group. Where missing values are imputed (*Table 52*), the EQ-5D results indicate higher mean EQ-5D scores throughout for the surgically treated group, although the differences are not statistically significant at any time point.

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TABLE 53 *Comparison of mean resource use for Group 3 over 0–24 months*

Type of care	Conservative: mean (SD) *n* = 122	Surgery: mean (SD) *n* = 124
Retreatment	*n* = 42	*n* = 5
Hospital in-patient admissions	–	0.073 (0.640)
Hospital outpatient visits	–	0.073 (0.449)
Accident and emergency visits	–	–
Anticoagulation clinic visits	–	–
GP visits[a]	0.057 (0.234)	0.210 (0.465)
Practice nurse visits	0.057 (0.234)	0.040 (0.918)
Visits to other health care professionals	0.082 (0.275)	0.057 (0.232)

[a] Significant difference in means at the 5% level.

TABLE 54 *Mean NHS costs of healthcare resource use for treatment for varicose veins, 0–24 months – Group 3*

Type of care	Conservative: mean (SD) (£) *n* = 122	Surgery: mean (SD) (£) *n* = 124
Initial treatment[a]	8.00 (0.00)	642.66 (236.39)
Retreatment[a]	251.31 (348.27)	29.44 (144.18)
Hospital admissions/visits	–	27.46 (181.62)
GP visits[a]	1.18 (5.51)	3.10 (6.67)
Practice nurse visits	0.85 (5.01)	0.65 (3.62)
Visits to other healthcare professionals	6.18 (46.16)	2.11 (16.46)
Total NHS costs[a] (undiscounted)	267.52 (350.91)	705.42 (276.95)
Total NHS costs[a] (discounted)	262.07 (346.82)	689.91 (260.23)

[a] Significant difference in means at the 5% level.

Cost-effectiveness analysis

As was found with Group 1, the number of patients in Group 2 was too small to undertake meaningful cost-effectiveness analysis. This issue is considered by the economic model in Chapter 6.

Group 3 trial

Costs

Table 53 shows the resources used by Group 3 during the 0-24-month period (excluding the resource use items associated with the initial treatment). There were statistically significant differences only for the number of GP visits, with those patients receiving surgery reporting a greater frequency of GP visits. Five patients who were randomised to receive surgical treatment initially received conservative treatment first and received surgery as a retreatment whereas 42 patients who were initially randomised to receive conservative treatment went on to receive surgical retreatment.

Table 54 documents the mean NHS costs for Group 3 during the first 24 months of the trial. It can be seen that there were statistically significant differences in the costs of the initial and retreatments received, GP visits and in total NHS costs. As expected, total mean NHS costs per patient were much higher for the surgically treated group.

Health outcomes: SF-6D

For Group 3 (*Table 55*), there is a deterioration in HRQoL measured according to the SF-6D between 0 and 1 month for both treatment groups (although the reduction is more marked in the surgically treated group and the differences are statistically significant). Over the 6–24-month period, the health status of the surgically treated group is higher than that of the conservatively treated group and the differences are statistically significant. Overall, the QALY gain at 24 months is higher for the surgically treated group, although the differences in QALY gain between treatment groups is not statistically significant. Where missing values are imputed (*Table 56*), the results are broadly similar to the base-case analysis, although the reduction in HRQoL between 0 and 1 month is less pronounced for the surgery group.

TABLE 55 *Group 3 SF-36 scores translated into SF-6D (original data)*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.741 (0.108) *n* = 103	0.733 (0.104) *n* = 95	0.017	–0.004 to 0.040
1 month[a]	0.609 (0.089) *n* = 81	0.587 (0.096) *n* = 53	0.024	0.009 to 0.045
6 months[a]	0.716 (0.116) *n* = 72	0.770 (0.117) *n* = 37	–0.049	–0.078 to –0.021
12 months[a]	0.727 (0.113) *n* = 98	0.769 (0.099) *n* = 75	–0.034	–0.058 to –0.011
24 months[a]	0.723 (0.129) *n* = 47	0.783 (0.099) *n* = 44	–0.409	–0.077 to –0.044
Area under curve from 0 to 12 months	0.699 (0.097) *n* = 52	0.711 (0.095) *n* = 28	–0.012	–0.057 to 0.033
Area under curve from 0 to 24 months (discounted)	1.443 (0.209) *n* = 31	1.498 (0.192) *n* = 20	–0.054	–0.171 to 0.062

[a] Significant difference in means at the 5% level.

TABLE 56 *Group 3 SF-36 scores translated into SF-6D (imputing data for missing values)*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.741 (0.108) *n* = 103	0.733 (0.104) *n* = 95	0.008	–0.022 to 0.038
1 month	0.637 (0.110) *n* = 107	0.639 (0.120) *n* = 79	–0.002	–0.035 to 0.032
6 months[a]	0.708 (0.113) *n* = 101	0.746 (0.108) *n* = 76	–0.038	–0.071 to –0.005
12 months[a]	0.727 (0.114) *n* = 100	0.768 (0.102) *n* = 79	–0.041	–0.073 to –0.009
24 months[a]	0.722 (0.125) *n* = 57	0.785 (0.101) *n* = 53	–0.626	–0.106 to –0.024
Area under curve from 0 to 12 months	0.696 (0.099) *n* = 91	0.724 (0.091) *n* = 66	–0.028	–0.059 to 0.002
Area under curve from 0 to 24 months (discounted)[a]	1.420 (0.205) *n* = 53	1.503 (0.168) *n* = 41	–0.083	–0.162 to –0.005

[a] Significant difference in means at the 5% level.

Health outcomes: EQ-5D

The results from the analysis of the EQ-5D for Group 3 differ from those for the SF-6D in that there is an initial improvement in HRQoL measured according to the EQ-5D between 0 and 1 month for both treatment groups (*Table 57*). Over the 6–12-month period the health status of the surgically treated group is higher than that of the conservatively treated group and the differences are statistically significant. As in the case of the SF-6D results, the QALY gain for the surgically treated group is slightly higher than that for the conservatively treated group. Where missing values are imputed (*Table 58*), the results are similar to the base-case analysis.

Cost-effectiveness analysis

For Group 3, it was found that there were some differences in both costs and outcomes between surgery and conservative treatment. Over the

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TABLE 57 *Group 3 EQ-5D scores (original data)*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.773 (0.183) *n* = 102	0.763 (0.190) *n* = 98	0.010	–0.042 to 0.062
1 month	0.838 (0.166) *n* = 83	0.825 (0.187) *n* = 53	0.013	–0.047 to 0.074
6 months[a]	0.799 (0.173) *n* = 72	0.890 (0.131) *n* = 36	–0.091	–0.155 to –0.026
12 months[a]	0.780 (0.178) *n* = 101	0.870 (0.135) *n* = 78	–0.091	–0.138 to –0.043
24 months	0.846 (0.165) *n* = 44	0.840 (0.208) *n* = 34	0.006	–0.079 to 0.091
Area under curve from 0 to 12 months	0.829 (0.144) *n* = 52	0.864 (0.112) *n* = 29	–0.035	–0.096 to 0.027
Area under curve from 0 to 24 months (discounted)	1.662 (0.209) *n* = 31	1.748 (0.223) *n* = 19	–0.086	–0.224 to 0.052

[a] Significant difference in means at the 5% level.

TABLE 58 *Group 3 EQ-5D scores (imputing data for missing values)*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Baseline	0.773 (0.183) *n* = 102	0.763 (0.190) *n* = 198	0.010	–0.042 to 0.062
1 month	0.814 (0.182) *n* = 107	0.797 (0.201) *n* = 80	0.017	–0.039 to 0.072
6 months[a]	0.785 (0.172) *n* = 102	0.852 (0.158) *n* = 75	–0.067	–0.117 to –0.017
12 months[a]	0.781 (0.178) *n* = 103	0.872 (0.135) *n* = 79	–0.091	–0.138 to –0.043
24 months	0.819 (0.199) *n* = 57	0.863 (0.193) *n* = 45	–0.043	–0.121 to 0.034
Area under curve from 0 to 12 months	0.804 (0.144) *n* = 92	0.837 (0.149) *n* = 69	–0.033	–0.081 to 0.014
Area under curve from 0 to 24 months (discounted)[a]	1.615 (0.299) *n* = 54	1.748 (0.242) *n* = 37	–0.133	–0.251 to 0.016

[a] Significant difference in means at the 5% level.

period of the trial it was found that surgery was associated with a significantly higher cost but with a slight increase in QALYs gained. As a consequence, the mean ICER for surgical treatment of varicose veins in patients with BK or AK varicosities with evidence of saphenofemoral or saphenopopliteal reflux is positive (*Table 59*; SF-6D). To gain an understanding of the uncertainty surrounding the ICER, a cost-effectiveness acceptability curve (CEAC) was estimated using a bootstrap method for the base-case data. The percentiles from the bootstrap repetitions were used to produce a CEAC. This shows the percentage of bootstrap repetitions that are cost-effective, assuming different ceiling values for the cost per QALY. Assuming an implicit threshold maximum WTP value of £30,000 for a QALY, *Figure 15* illustrates that using the SF-6D as the measure of outcome, the probability of the cost per QALY of surgical treatment for varicose

TABLE 59 *Summary of outcome and NHS costs using SF-6D*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Mean NHS cost over 24 months (discounted) (£)[a]	328.10 (360.87) $n = 31$	715.54 (184.00) $n = 20$	–387.45	–563.08 to –211.81
Mean NHS cost over 24 months (discounted) (£)[1a]	344.53 (357.47) $n = 53$	733.10 (134.99) $n = 41$	–388.57	505.52 to –281.99
Area under the curve SF-6D, 0 to 24 months (discounted)	1.443 (0.209) $n = 31$	1.498 (0.192) $n = 20$	–0.054	–0.171 to 0.062
Area under the curve SF-6D, 0 to 24 months (discounted)[1a]	1.420 (0.205) $n = 53$	1.503 (0.168) $n = 41$	–0.083	–0.162 to –0.005
ICER[c]			7175 4682[b]	4539–23,712 2039–20,830

[a] Significant difference in means at the 5% level.
[b] Imputed data for missing SF-6D values using straight-line interpolation.
[c] 95% CI estimated using the 5th and 95th percentiles of the bootstrap repetition ICER values.

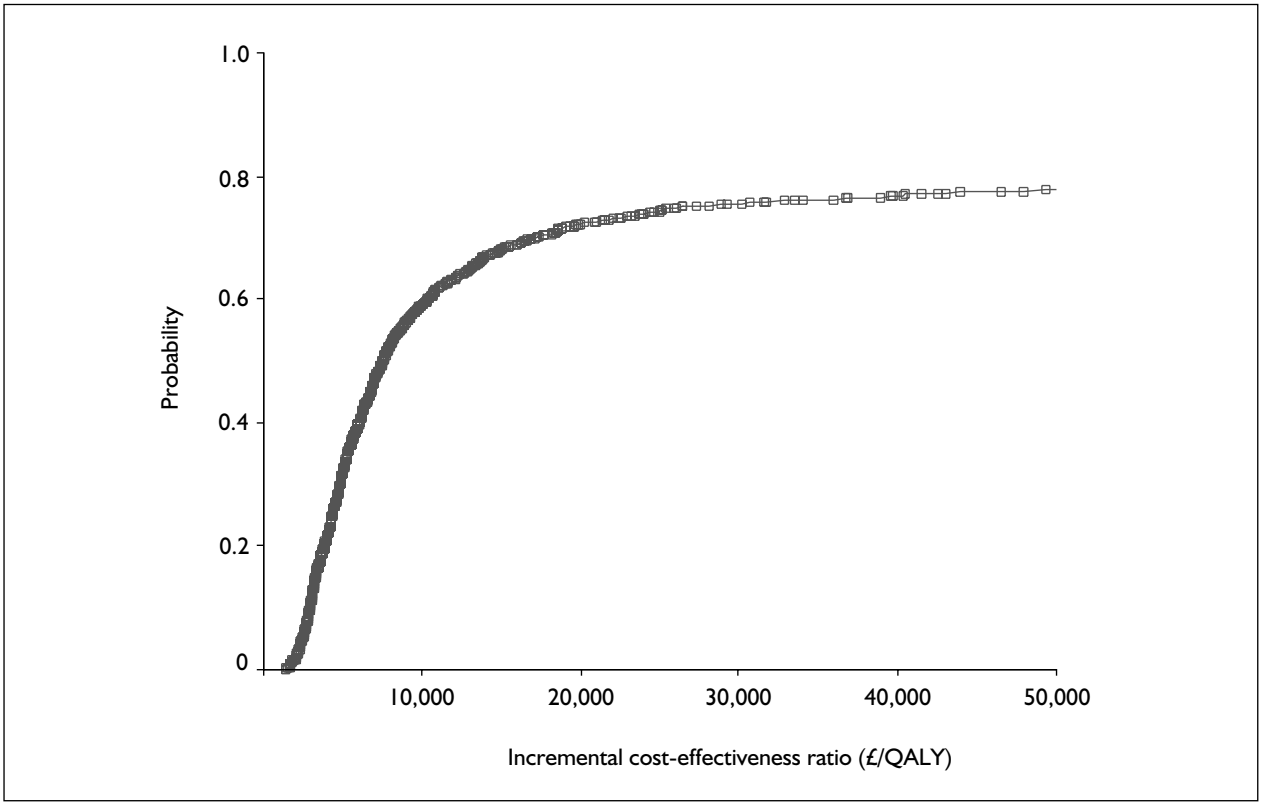

FIGURE 15 *CEAC using SF-6D*

veins falling below this threshold value is approximately 75–80%.

The distribution of the ICER estimates resulting from the bootstrap repetitions using the SF-6D as the measure of outcome is shown in *Figure 16*. It can be seen that the majority of observations indicate that surgical treatment for varicose veins results in increased costs and improved effectiveness relative to conservative treatment.

The results of the cost-effectiveness analysis using the EQ-5D as the outcome measure are presented in Appendix 4. The results of this analysis are very similar to those obtained using the SF-6D to estimate QALYs.

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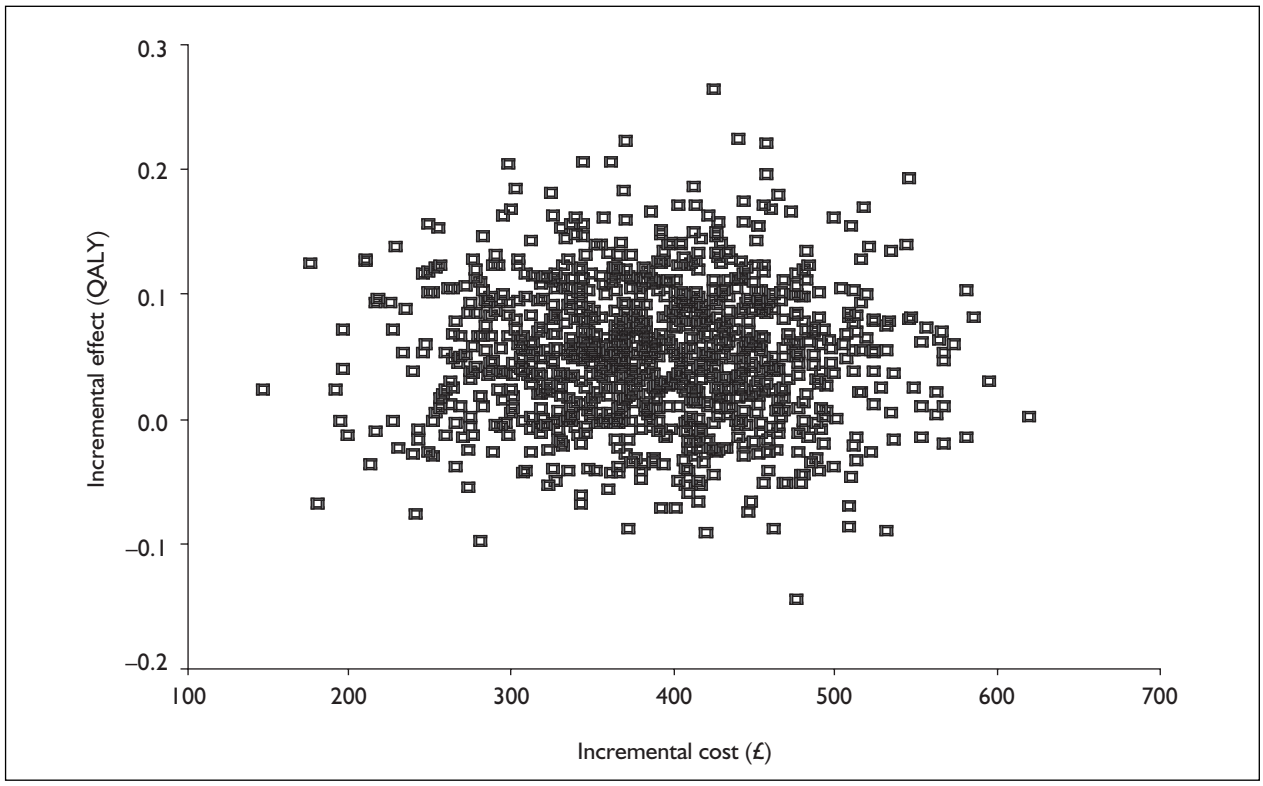

FIGURE 16 *Plot of distribution of bootstrapped ICER estimates using SF-6D*

Alternative cost-effectiveness analyses

A number of alternative analyses of cost-effectiveness were carried out to test assumptions made in the main analysis and to improve the generalisability of the results, including:

- using the EQ-5D to calculate QALYs
- using mean NHS reference cost for surgical treatment for varicose veins rather than local unit cost
- using the lower quartile of NHS reference cost for surgical treatment for varicose veins
- using the upper quartile of NHS reference costs for surgical treatment for varicose veins.

The results of these analyses are provided in Appendix 4. None of the alternative assumptions had a significant impact and the ICER values obtained were broadly similar to that obtained from the base-case analysis.

Patient preference: willingness to pay study

Background

WTP, also known as contingent valuation, is a method of measuring the impact of a condition on HRQoL in terms of how much patients are willing to pay, in monetary terms, to be free of the condition.[191] WTP, although originally developed to value changes in the environment, has been widely used in healthcare to elicit public views in areas including antenatal care,[192] water fluoridation[193] and psoriasis.[194] One of the potential advantages of WTP over other methods of measuring HRQoL is that it can also incorporate aspects of benefit such as information and cosmetic outcomes.

Methods

Following ethic committee approval to administer the WTP questionnaire, 100 patients at each of the participating sites (Sheffield and Exeter) were asked to complete it. The patients were selected from those patients who had been referred by their GP to the vascular unit with a probable diagnosis of primary varicose veins and who were on the waiting list for an outpatient appointment.

The participants were sent the WTP questionnaire with a covering letter and a participant information sheet with their outpatient appointment. They were then asked to complete the questionnaire and bring it with them when they attended for their outpatient appointment. Emphasis was placed on the voluntary nature of the survey and on the participants' right to not participate in the study should they choose not to do so.

The WTP questionnaire consisted of scenarios describing typical patients with mild, moderate and severe varicose veins (see Appendix 5). The participants were presented with the treatment options for these states and asked to indicate either a preference for treatment A or treatment B or indifference between the treatments. Where they chose one of the treatments, they were asked to indicate the maximum they would be willing to pay for their preferred choice. The participants were told that the payments were entirely hypothetical and that there would be no question of them actually having to pay.

One problem that can arise with WTP is that previous studies where patients have been asked to value treatments within the context of a clinical trial have failed to discriminate between the treatment alternatives offered.[195,196] It has been hypothesised that this is due to patients within the trial valuing only the care they have had and not the alternative treatments.[195] Therefore, it has been recommended that when using WTP alongside clinical trials, as is the case with the current study, values should be elicited from patients[192] on the basis of the preferred treatment to allow the marginal monetary valuation of receiving the preferred treatment to be elicited. This approach was adopted for this study.

Data analysis

The main data analysis included an estimation of the proportions that selected each choice and amongst those who selected a treatment a single sample chi-squared test was undertaken. Basic descriptive statistics were calculated from the WTP data. Secondary analysis included an ANOVA to estimate the impact of respondent background characteristics (such as age, health and income) on WTP.

Results

An overall response rate of 32.5% ($n = 65$) was achieved. *Table 60* details the characteristics of the respondents. It can be seen that the majority (72%) of respondents were female. Approximately 49% of respondents had not received previous treatment for their varicose veins. The age distribution was more heavily weighted towards those in older age groups and this is reflected in occupational status (with 26% of respondents indicating that they were retired from employment) and in income levels (which was more heavily weighted towards those in lower income brackets). Despite their varicose veins diagnosis, 55% of respondents rated their health as either excellent or very good and only one respondent considered their health to be poor.

Table 61 indicates respondent preferences in relation to treatment for mild, moderate and severe varicose veins. It can be seen that conservative treatment was favoured by the majority of respondents for mild varicose veins. The mean WTP to receive conservative treatment was £85.90 and £76.20 for sclerotherapy. The difference between the mean values was not statistically significant. For moderate varicose veins, respondents were fairly evenly split in terms of their preference to receive either surgery or sclerotherapy. The mean WTP to receive surgery was higher than for sclerotherapy (£508.97 versus £270.43), although the difference in mean values was not statistically significant. In the case of treatment for severe varicose veins, the majority of respondents indicated that they would have a preference to receive surgery (only one respondent indicated that they would prefer to receive conservative treatment). The mean WTP to receive surgery for severe varicose veins was £656.34.

Tables 62–64 indicate the relationship between respondent characteristics and WTP values using an ANOVA test. It can be seen that for mild varicose veins (*Table 62*) there are statistically significant differences between WTP values according to education level and income level, with WTP for preferred treatment being positively associated with respondents' education and income levels. However, there were no statistically significant differences between respondent characteristics and WTP for preferred treatment for moderate or severe varicose veins respectively.

Key points

- Surgical treatment for varicose veins associated with reflux offers a modest health benefit for a small additional NHS cost relative to conservative treatment. This conclusion is robust over a range of alternative assumptions relating to unit costs for varicose vein treatments.
- The consideration of a longer time horizon is likely to reduce the ICER for surgery.
- If £30,000 per QALY is taken as the maximum acceptable cost-effectiveness ratio, then on the basis of these results for patients with severe varicose veins, surgical treatment appears highly cost-effective.
- The results for sclerotherapy for minor varicose veins were insufficient for cost-effectiveness analysis and were examined by economic modelling.

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TABLE 60 *Respondent characteristics (n = 65)*

	Frequency	%
Gender		
Male	18	27.7
Female	47	72.3
Age group (years)		
<30	1	1.5
31–40	11	16.9
41–50	15	23.1
51–60	19	29.2
61–70	15	23.1
>70	4	6.2
Previous treatment		
Yes	33	50.8
No	32	49.2
Occupation		
Retired	17	26.2
Administration/secretarial	12	18.5
Housewife	10	15.4
Healthcare	5	7.7
Manager	5	7.7
Education	4	6.2
Unemployed	2	3.1
Police	2	3.1
Other	8	12.3
Dependent children		
0	40	61.5
1	6	9.2
2	10	15.4
3	7	10.8
4	2	3.1
Education		
Primary	9	13.8
Secondary	32	49.2
A-level	9	13.8
University	9	13.8
Other	4	6.2
Missing	2	3.1
Health		
Excellent	11	16.9
Very good	32	47.7
Good	16	24.6
Fair	6	9.2
Poor	1	1.5
Income (£)		
<£5000	15	23.1
£5000–£9999	17	26.2
£10,000–£14,999	10	15.4
£15,000–£19,999	7	10.8
£20,000–£24,999	3	4.6
£25,000–£30,000	5	7.7
>£30,000	3	4.6
Missing	5	7.7

TABLE 61 *Preference and WTP for treatment for varicose veins*

Preference	Frequency	%
Mild varicose veins		
Conservative	40	61.5
Sclerotherapy	17	26.2
Equal	8	12.3
$\chi^2 = 9.28$, $p = 0.002$		
WTP conservative treatment, $n = 39$	Mean WTP: £85.90[a] SD: £181.48 Median WTP: £20.00 IQ range: £20–75 Range: £0–1000	
WTP sclerotherapy $n = 17$	Mean WTP: £76.25[a] SD: £65.31 Median WTP: £100.00 IQ range: £15–100 Range: £0–200	
Moderate varicose veins		
Surgery	29	44.6
Sclerotherapy	27	41.5
Equal	8	12.3
Missing	1	1.5
$\chi^2 = 0.071$, $p = 0.789$		
WTP Surgery $n = 29$	Mean WTP: £508.97[a] SD: £739.09 Median WTP: £300.00 IQ range: £100–500 Range: £0–3000	
WTP Sclerotherapy $n = 23$	Mean WTP: £270.43[a] SD: £316.82 Median WTP: £200.00 IQ range: £50–300 Range: £0–1000	
Severe varicose veins		
Surgery	57	87.7
Conservative treatment	1	1.5
Equal	5	7.7
Missing	2	3.1
$\chi^2 = 54.07$, $p < 0.001$		
WTP surgery $n = 56$	Mean WTP: £656.34[a] SD: £1236.93 Median WTP: £300.00 IQ range: £100–500 Range: £0–7500	
WTP conservative treatment, $n = 1$	Mean WTP: £20.00[a] SD: – Median WTP: £20.00 IQ range: £20–20 Range: £20–20	

IQ, interquartile.
[a] Differences between means were not statistically significant.

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TABLE 62 *Relationship between respondent characteristics and WTP for preferred treatment – mild varicose veins*

Age group (years)	**<40**	**41–50**	**51–60**	**>60**
N Mean WTP (SD) (£) *p* = 0.501	10 46.50 (46.43)	11 101.82 (113.98)	17 123.82 (235.07)	16 52.81 (121.93)
Gender	**Male**	**Female**		
N Mean WTP (SD) (£) *p* = 0.954	15 86.00 (124.85)	39 83.20 (170.00)		
Received previous treatment	**Yes**	**No**		
N Mean WTP (SD) (£) *p* = 0.125	31 112.42 (201.18)	23 45.65 (44.45)		
Dependent children	**Yes**	**No**		
N Mean WTP (SD) (£) *p* = 0.330	19 112.63 (222.86)	35 68.43 (108.25)		
Education[a]	**Primary**	**Secondary**	**A-level**	**University**
N Mean WTP (SD) (£) *p* = 0.026	8 48.13 (38.91)	28 47.32 (54.63)	8 109.38 (166.18)	7 242.86 (360.68)
Health	**Excellent**	**Very good**	**Good**	**Fair/poor**
N Mean WTP (SD) (£) *p* = 0.218	10 74.00 (120.66)	27 52.41 (58.81)	13 163.08 (284.18)	4 65.00 (72.34)
Income[a]	**<5000**	**5000–9999**	**10,000–19,999**	**>20,000**
N Mean WTP (SD) (£) *p* = 0.025	11 31.82 (48.13)	14 42.86 (£57.13)	15 78.33 (99.69)	10 219.00 (308.89)

[a] Statistically significant differences between means.

TABLE 63 *Relationship between respondent characteristics and WTP for preferred treatment – moderate varicose veins*

Age group (years)	**<40**	**41–50**	**51–60**	**>60**
N Mean WTP (SD) (£) *p* = 0.662	10 536.00 (913.46)	13 330.77 (200.56)	14 278.57 (264.37)	15 494.67 (790.34)
Gender	**Male**	**Female**		
N Mean WTP (SD) (£) *p* = 0.426	17 307.65 (318.35)	35 450.00 (694.09)		
Received previous treatment	**Yes**	**No**		
N Mean WTP (SD) (£) *p* = 0.770	24 380.71 (578.93)	28 430.00 (630.83)		
Dependant children	**Yes**	**No**		
N Mean WTP (SD) (£) *p* = 0.483	21 331.90 (288.49)	31 451.94 (132.75)		
Education	**Primary**	**Secondary**	**A-level**	**University**
N Mean WTP (SD) (£) *p* = 0.792	8 195.00 (197.63)	24 430.00 (823.24)	8 456.25 (373.63)	8 456.25 (263.81)
Health	**Excellent**	**Very good**	**Good**	**Fair/poor**
N Mean WTP (SD) (£) *p* = 0.509	8 606.25 (990.11)	27 422.22 (577.18)	12 355.83 (407.71)	5 92.00 (87.01)
Income	**<£5000**	**£5000–9999**	**£10,000–19,999**	**>£20,000**
N Mean WTP (SD) (£) *p* = 0.142	8 138.75 (160.84)	15 691.33 (999.09)	15 283.33 (253.31)	10 410.00 (273.66)

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TABLE 64 *Relationship between respondent characteristics and WTP for preferred treatment – severe varicose veins*

Age group (years)	**<40**	**41–50**	**51–60**	**>60**
N Mean WTP (SD) (£) *p* = 0.722	12 990.42 (2116.49)	13 703.85 (1320.90)	15 466.67 (460.46)	16 545.00 (656.40)
Gender	**Male**	**Female**		
N Mean WTP (SD) (£) *p* = 0.450	17 465.29 (470.01)	39 739.62 (1448.45)		
Received previous treatment	**Yes**	**No**		
N Mean WTP (SD) (£) *p* = 0.946	28 645.00 (1044.54)	28 667.68 (1423.14)		
Dependant children	**Yes**	**No**		
N Mean WTP (SD) (£) *p* = 0.890	22 685.23 (1085.20)	34 637.65 (1341.51)		
Education	**Primary**	**Secondary**	**A-level**	**University**
N Mean WTP (SD) (£) *p* = 0.737	9 317.78 (100.95)	28 828.39 (1686.12)	8 506.25 (689.95)	7 521.43 (380.63)
Health	**Excellent**	**Very good**	**Good**	**Fair/poor**
N Mean WTP (SD) (£) *p* = 0.562	8 596.88 (362.17)	29 859.31 (1587.35)	13 476.92 (491.01)	6 143.33 (166.93)
Income	**<£5000**	**£5000–9999**	**£10,000–19,999**	**>£20,000**
N Mean WTP (SD) (£) *p* = 0.118	12 294.17 (368.92)	16 1290.63 (2111.73)	15 408.33 (508.65)	10 475.00 (411.80)

Chapter 6

Cost-effectiveness modelling

Introduction

This chapter describes the development and results of an economic model for the treatment of varicose veins. There are a number of specific issues that the model will address:

- The effect of considering an extended time frame beyond that available in the clinical trial, to allow the effects of persisting benefits, progression of disease and retreatment to be taken into account in calculating expected cost-effectiveness.
- The effect of uncertainty around some of the parameters that are required to estimate cost-effectiveness. Specific issues include probability estimates for rare events (e.g. the rate of unusual but significant complications), parameters for which the value may be subject to uncertainty owing to issues around method of measurement (e.g. utility valuations) and parameters which may vary depending on the local setting (e.g. costs and case mix).
- The effect of different aspects of treatment protocols that were not tested in the RCTs. These include issues such as decisions around retreatment and the effect of differences in waiting times.
- The identification of important areas of uncertainty through sensitivity analysis, in order to guide recommendations regarding the key areas for further research.

The basic modelling technique and model structure will be described, followed by a general description of the data used for the different model parameters, including probabilities, costs and utilities. Following this, the details of individual models used to simulate specific clinical situations will be described in more detail with the results of the modelling.

Method

General structure of the model

A cost-effectiveness model was developed using a specialist software package (DATA Pro, TreeAge Software Inc.). A Markov decision tree was constructed, defining the possible transitions between the different clinical states that may occur in each period. The model was then populated with data regarding the probability of transition between states and the cost and utility associated with each transition or health state.

The time interval considered in the model was set at 1 month to correspond to the approximate timeframe of clinical changes and recovery period from various treatments. The model considered a time horizon of 120 time cycles (i.e. 10 years) for the base-case analysis. This time horizon was chosen as being in keeping with the available information from published literature regarding the results of clinical trials (see Chapter 2).

Definition of health states

The clinical states were based on the anatomical classification provided in Chapter 3. Although one could potentially use other methods of classifying states such as symptomatic measures of severity, it was considered that the anatomical classification corresponded most closely with the clinical trial and with the available treatment options. The Markov process relies on the principle that costs, utilities and probabilities associated with a specific clinical state are independent of previous treatment. As there is evidence that surgical intervention may slow the rate of progression/recurrence of the condition (see Chapter 2), additional 'post-operative' states were included.

Treatments were dealt with by having specific clinical states to represent sclerotherapy, surgery and redo surgery. Patients undergoing these treatments remain in the appropriate state for a single time cycle, and this allows any effect on utility or cost to be associated with that specific treatment. Additional states were included for the results of successful sclerotherapy, the complications of sclerotherapy and surgery, co-morbidity (to allow for patients who might develop other diseases or complications that would make them unsuitable for the treatment options or where the disutility would outweigh any effects of varicose veins) and an absorbing state for death.

This resulted in a general model with the 16 health states described in *Table 65*.

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TABLE 65 *Description of health states used in the Markov model*

State	Description	Notes
G1-U	Group 1 – unoperated	Minor varicose veins in Group 1 based on classification in Chapter 3 (lower thigh and <2 quadrants of calf, without reflux)
G2-U	Group 2 – unoperated	Moderate varicose veins in Group 2 based on classification in Chapter 3 (lower thigh and <2 quadrants of calf, with reflux)
G3-U	Group 3 – unoperated	Severe varicose veins in Group 3 based on classification in Chapter 3 (thigh and >2 quadrants of calf)
Sclero	Undergoing sclerotherapy	State for 1-month time cycle of sclerotherapy treatment
Surg	Undergoing surgery	State for 1-month time cycle of surgery treatment
Sclero-S	Sclerotherapy success	State following successful sclerotherapy
Sclero-C	Sclerotherapy complication	State following the development of a persistent complication of sclerotherapy
As-P	Asymptomatic after surgery	No symptoms of varicose veins following surgery
G1-P	Group 1 – postoperative	Minor varicose veins in Group 1 (as above) based on worst leg following surgery to one or both legs
G2-P	Group 2 – postoperative	Moderate varicose veins in Group 2 (as above) based on worst leg following surgery to one or both legs
G3-P	Group 3 – postoperative	Severe varicose veins in Group 3 (as above) based on worst leg following surgery to one or both legs
Surg-R	Undergoing redo surgery	State for 1-month time cycle of redo surgery treatment
Surg-CMin	Surgery complication – minor	State following the development of a persistent minor complication of surgery
Surg-CMaj	Surgery complication – major	State following the development of a persistent major complication of surgery
Co-morb	Co-morbidity	State of co-morbidity (excluded from further consideration owing to development of complication or other condition that would preclude trial choices for the treatment of varicose veins)
Dead	Dead	Absorbing state to represent general and procedure-related mortality

Modelling complications

The development of complications may have significant cost and outcome implications. For the purpose of the model, complications were divided into a number of different categories depending on whether they are transient or persistent and minor or major.[197] Those complications that are transient in nature, such as wound infections and haematoma following surgery, and blistering or ulceration following sclerotherapy, are included in the estimation of cost and outcome values attributed to the temporary states representing those treatments. Although some of these complications may persist for more than 1 month, the effect of this simplification on the overall cost effectiveness is likely to be minimal.

In terms of persistent complications, separate states have been identified for complications of sclerotherapy (such as skin pigmentation) and for the complications of surgery, which have been subdivided into minor (e.g. areas of paraesthesia) and major (e.g. DVT, pulmonary embolus and motor nerve damage).

Assumptions

For each clinical state, a set of probabilities has been identified for the possible outcomes of that state along with costs and utilities associated with the state and transitions. This involves a number of assumptions and simplifications.

- It is assumed that the anatomical extent of varicose veins will not improve without treatment by either surgery or sclerotherapy. Hence the probability of transition from any group directly to a lower group or an asymptomatic state is zero.
- The development of varicose veins is assumed to take place stepwise from asymptomatic to Group 1, to Group 2, to Group 3, without patients jumping state. With a period of

1 month, it is likely that this is a reasonable assumption.
- In the initial base-case model, the development of co-morbidity and death rate are considered to be independent of the severity of the varicose veins. This may raise particular issues in relation to the development of venous ulceration. At present there is no published evidence to determine clearly whether treatment of varicose veins by surgery or sclerotherapy has any significant effect on the probability of subsequent development of skin changes and ulceration. Any significant effect in this respect may have considerable implications for the cost-effectiveness of varicose vein treatment, owing to the high costs and considerable effects on HRQoL that are associated with this condition.[198] The model has therefore been set up in such a way that it will allow the implications of this assumption to be tested by carrying out a sensitivity analysis using different risks of complications and co-morbidities for the different health states represented by the model.
- Although primary and redo surgery are treated separately, there is no separation of third or subsequent redo procedures. It was considered that there are insufficient data to identify separate probabilities or costs for separate states to represent these.
- Some assumptions need to be made in determining how the model deals with patients who have bilateral varicose veins. For the purpose of the clinical trial, the condition of the patient and the randomisation were based on the index limb, being the limb defined by the patient as having the more severe symptoms. Costs and utilities recorded in the clinical trial include the effect of symptoms and treatments relating to both limbs. The approach taken in the modelling is to base all states upon the worst limb at the time and include all costs relating to the treatment of both legs. Since the evidence suggests that surgical treatment reduces the rate of progression of varicose veins, this requires the simplification of taking average recurrence rates for patients with previous treatment of either one or both legs. The alternative would be to have a separate state for each combination of severity (e.g. 'left – Group 1 untreated/right – Group 2 postoperative'). This would require over 200 separate states and the data are not available to derive separate probabilities, costs and utilities for all the possible states and transitions.
- For the base-case analysis, it is assumed that where both limbs undergo surgery or sclerotherapy, the entire treatment is carried out within the 1-month time cycle of the model. In practice this is not always the case as some centres carry out bilateral surgery as staged unilateral day-case procedures.
- The base-case analysis assumes that all initial treatments are carried out immediately at the start of the modelling period. In practice there may be delays in undertaking some treatments owing to waiting lists, and the effect of this is considered in the sensitivity analysis.

Probabilities

The probabilities required for the model fall into two main groups. First there are probabilities that are the result of chance events and these may be obtained through clinical trials, observational data or expert opinion. These probabilities include the rate of progression of varicose veins, the risk of complications and mortality. These figures were obtained from the clinical trial wherever possible, supplemented by literature reviews of the published results of other clinical trials. *Table 66* provides details of the probabilities used in the model, along with the source of the data.

The second group of probabilities that are required relate to treatment choices and are therefore dependent on the clinical decision-making and policy regarding the use of various interventions. These differ in the modelling of the individual arms of the clinical trials and the assumptions will be described below.

One of the key issues in terms of probabilities is the rate of progression of varicose veins. Detailed information in this respect is not available from the clinical trial reported in Chapter 4, owing to the limited length of follow-up. However, there are a number of publications summarised in the literature review (Chapter 2) that provide estimates of these parameters. Since the reporting within these trials does not allow categorisation of patients into the anatomical states described in the computer model, it has been necessary to estimate these figures and to assess the validity of these estimates by comparing the implications of the model with published clinical data and the data from the clinical trial.

The clinical evidence suggests that adequate surgery, including the treatment of valvular incompetence, reduces the rate of progression/recurrence of varicose veins. In order to model this it has been assumed that there are two rates of progression, with a lower rate of progression amongst those patients without

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TABLE 66 *General probabilities used in the base case for the economic model*

Description	Base case (%)	Comment	Sources
Probability of progression without reflux	20.0	Assume constant progression rate for states without reflux (i.e. Group 1 and asymptomatic or Group 1 postoperatively and after successful sclerotherapy in Model 1 – see text)	Clinical trial and systematic review
Probability of progression with reflux	25.0	Assume constant progression rate for states with reflux (i.e. Group 2 to 3 pre- and postoperative and after successful sclerotherapy in Model 2 – see text)	Clinical trial and systematic review
Probability of developing co-morbidity	1.0	Approximate figure based on those in clinical trial who developed contra-indications to treatment	Clinical trial
General mortality	Related to age	Based upon Mortality Tables for England and Wales using median age of trial recruits	DH mortality tables[199]
Surgical mortality	0.001	Base case 1:100,000	HES data for England and Wales
Probability of surgery resulting in postoperative Group 1	10.0	Clinical trial suggests 10% of patients have residual veins, without reflux after surgery	Clinical trial
Probability of a major complication of surgery	0.8	Data from trial based on persistent complications (the effect of transient complications are included in treatment groups)	Literature review and clinical trial
Probability of a minor complication of surgery	6.6	As above	Literature review and clinical trial
Probability of a complication following sclerotherapy	10.3	Probability of being troubled by staining at 1 year (see Chapter 4)	Clinical trial

DH, Department of Health.

valvular incompetence (i.e. in Group 1 prior to treatment or those who are asymptomatic, or in Group 1 following surgery), with a higher rate for those who are in Group 2 before or after surgery. For the purposes of the model, these probabilities are represented as a probability of progression in the absence of reflux and an increment to be added to this to represent the higher rate of progression in those with reflux. This allows sensitivity analysis to be carried out on the difference between the two rates.

Mortality was taken from Mortality Tables for England and Wales[199] with a starting age equivalent to the median age in the clinical trial, with adjustment for age at each cycle of the model.

Costs

The costs for the various treatments included in the model are those identified in the economic analysis in Chapter 5. As described above, complications have been divided into transient/persistent and major/minor. The estimated costs from the clinical trial have been apportioned so that those related to early transient complications are included in the cost of the initial treatment. The remaining costs of complications are apportioned to the specific states representing those complications. The costs of initial treatment also include any costs associated with the initial treatment of the second limb, as discussed above. *Table 67* provides details of the point estimates of costs used in the base case of the model. This method results in costs that do not exactly correspond to those in Chapter 5.

In keeping with UK Department of Health guidelines,[184] the discount rate that is used for both costs and utilities has been set at 3.5%, with a sensitivity analysis being carried out between 0% and 7%.

All costs have been assessed from an NHS perspective and, for the base-case analysis, it has been assumed that there are no ongoing costs

TABLE 67 *Costs used in the base case for the economic model*

Description	Value	Comment	Source
Cost of surgery	785	Includes cost contribution for some second operations (staged bilateral) and transient complications (see text)	Clinical trials
Cost of sclerotherapy	160	Includes cost contribution for transient complications	Clinical trials
Cost of developing a major surgical complication	1387	The total is assumed to include all 'one time only' costs associated with persistent complications, although some costs may be incurred outside the first month	Clinical trials
Cost of developing a minor surgical complication	91	As above	Clinical trials
Cost of having a major surgical complication (per month)	0	In clinical trials there were no ongoing costs (except those early costs which are included in cost of developing a complication)	Clinical trials
Cost of having a minor complication (per month)	0	No evidence of ongoing costs	Clinical trials
Cost of developing a complication of sclerotherapy	0	Cost of short-term complications and early GP visits, etc., included in cost of treatment. No costs were identified associated with long-term complications	Clinical trials
Cost of state of co-morbidity	0	The base case ignores costs as the rate of comorbidity is equal for all groups so there is no effect on incremental cost-effectiveness – for sensitivity analysis dealing with possibility of greater rate of ulceration in Group 3 an estimated cost of ulcer treatment is used	Ref. 198
Cost of being in Group 1	0	No evidence of ongoing costs	Clinical trials
Cost of being in Group 2 or 3	0	No evidence of ongoing costs, sensitivity analysis considers prescription of stockings (see text)	Ref. 187
Discount rate for costs	0.035	Based on DH guidance	Ref. 184

associated with any of the clinical states of varicose veins. The only ongoing cost that was identified in the clinical trial was the cost of continuing compression hosiery. This continued to be used by only 16% of patients with varicose veins within the study, and the majority of these purchased their own compression hosiery rather than relying on those products that were available on prescription. These costs have been considered in the sensitivity analysis.

Utilities

The utilities used in the model are based on the outcome analysis carried out in the clinical trial. At the time of recruitment there were no significant differences between the utility scores for patients in the different clinical categories. Possible explanations for this are discussed in Chapter 7. There are, however, significant improvements in patients associated with treatment, with patients who were in a less severe anatomical group having significantly higher utilities at 1 year (see Chapter 5). Owing to these problems, it is not possible to use the recruitment utilities as estimates for the utilities for individual clinical groups within the model. The only utility data available that provide comparable estimates of utility and can be correlated with the clinical grouping in the trial are those obtained at the 1-year follow-up (reported in Chapter 5). These suggest that, based on averaging EQ-5D and SF-6D data, the utility for a patient in Group 3 is 0.76 and for a patient who is asymptomatic following treatment it is 0.85, with intermediate values for Groups 1 and 2. The full details of utility scores used as a base case for the analysis are provided in *Table 68*.

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TABLE 68 *Utilities used in the base case for the economic model*

Description	Value	Comment	Source
Utility of being asymptomatic	0.85	Base-case figures from average of SF-6D and EQ-5D from clinical trial	Clinical trials
Utility of being in Group 1	0.82	Estimated for intermediate states – see text	Clinical trials
Utility of being in Group 2	0.79	Estimated for intermediate states – see text	Clinical trials
Utility of being in Group 3	0.76	Base case figures from average of SF-6D and EQ-5D from clinical trial	Clinical trials
Utility of surgical treatment	0.60	Based on SF-6D 1-month valuation (see text)	Clinical trials
Utility of redo surgery	0.60	As above – no evidence for differences between primary and redo surgery	Clinical trials
Utility of sclerotherapy	0.76	Set equivalent to Group 3	Clinical trials
Utility of state co-morbidity	0.70	Approximated based on published data for range of similar conditions and correlated with clinical groups for sensitivity analysis	Ref. 200
Utility of having sclerotherapy complication	0.79	Set equivalent to Group 2	Expert opinion
Utility of sclerotherapy success	0.85	Set equivalent to asymptomatic	Expert opinion
Utility of having a major surgical complication	0.76	Set equivalent to Group 3 and correlated in sensitivity analysis	Expert opinion
Utility of having a minor complication of surgery	0.82	Set equivalent to Group 1 and correlated in sensitivity analysis	Expert opinion
Discount rate for utilities	0.035	Discount rates for costs and utility set to be the same	Ref. 184

The sample size of the clinical trials was not sufficient to provide adequate estimates of the utilities associated with complications and co-morbidity. For the co-morbidity state, a value of 0.7 was taken, in keeping with published figures for conditions such as peripheral vascular disease and leg ulceration.[200] Utility valuations were correlated with those for the clinical states referred to above in order to prevent distortion in the univariate sensitivity analysis. Patients with a complication of sclerotherapy were assumed to have a utility at the same level as those in Group 2; for those with complications of surgery the level for a major complication was set at equivalent to those in Group 3 and for minor complications as equivalent to Group 1. For the time cycle during which patients underwent treatment, the utilities were set as 0.6 for surgery, based on the decrease seen in SF-6D scores at 1 month following surgery. The SF-6D was chosen rather than EQ-5D for this purpose owing to the methodology which relates valuation to the previous 4 weeks, rather than valuing the current situation. For sclerotherapy the value was set at a utility equivalent to that of patients in Group 3.

Sensitivity analysis and alternative strategies

The validity and robustness of the model were addressed through sensitivity analysis, and a number of alternative strategies and scenarios were considered. Univariate sensitivity analysis was carried out for each of the variables listed in *Tables 66–68*. Deliberately wide ranges were used in these analyses in order to identify those variables that have the greatest potential to influence the findings significantly. In carrying out sensitivity analysis on the probability of progression, the variables were defined as described above, with a rate for progression in the absence of reflux and an increment to be added to this to represent the higher rate of progression in those with reflux. Although there is evidence regarding the higher rate of recurrence in those with persistent reflux, and indirect evidence from the trials of stripping of the LSV (see Chapter 2), the nature of the evidence and classification of extent of veins do not allow accurate estimation of these parameters. Sensitivity analysis included a wide range of values, with progression rates without reflux from 15 to 25% and a difference

between 0 and 10% per year. All the ranges for sensitivity analysis are given below in the tables of results.

For cost data, the National Tariffs provide 'Market Forces Factors',[201] which use multipliers of 0.88–1.28 for tariff rates. However, reference costs suggest wider variation between NHS Trusts in the UK[201] and in addition there are differences in policy, such as the use of day-case procedures and staged procedures for bilateral cases, which may have further effects on cost. To cover all these potential sources of variability, a wide range of costs, from 50 to 200% of base case, was used for the univariate sensitivity analysis.

For utilities there is also a wide range of estimates, particularly relating to methodological differences in the technique used to elicit these. It is recognised that the ideal method of utility valuation is open to question and that accurate estimates are not available in the literature, so a wide range of values were tested in the sensitivity analysis. For the purpose of the sensitivity analysis, utilities were correlated to ensure that the rank order was maintained (asymptomatic, Group 1, Group 2, Group 3), with a minimum utility difference of 0.01 between adjacent values.

Multivariate sensitivity analysis was carried out using a second-order Monte Carlo simulation with a cohort size of 1000 using estimated distributions for the variables considered in the univariate analysis. Probabilities were assumed to have beta distributions based, where possible, on results from the clinical trial or from published reports. Costs were assumed to have a normal distribution and were also based on the results of the clinical trial. For utility estimation, the distribution for the asymptomatic state used a custom distribution based on the actual distribution of utilities seen in the clinical trial, with the range of differences being normally distributed.

Alternative situations were considered in the models to address potential differences in policy such as the use of redo surgery or further sclerotherapy, factors such as waiting time and time horizon and assumptions regarding co-morbidity and crossovers. The effects of varying discount rates between 0 and 7% were assessed, with the same rate being used to discount costs and utilities. The effect of differing age at the time of presentation was assessed between ages of 20 and 60 years. Further details of alternative analyses are given below with respect to individual models.

Model 1

Specific assumptions

The Model 1 simulation relates to the Group 1 clinical trial in which sclerotherapy was compared with conservative treatment. The influence diagram representing the Markov model for this trial is shown in *Figure 17*.

The assumptions made in this model are that patients who are initially treated conservatively will continue to be treated in this way and will not be offered sclerotherapy at any point in their treatment. They would however be offered surgical treatment if they were to deteriorate to Group 2 or 3, with the rate of uptake of surgical treatment being based on the evidence from the clinical trial for uptake of surgical treatment amongst those patients who were initially treated conservatively in Group 2 or 3.

For those patients who were treated with sclerotherapy, the base-case assumption was that there would be a single episode of sclerotherapy and that surgical treatment would be offered for those patients who deteriorate to Group 2 or 3 at the same rate as for those who were treated conservatively. It is assumed that sclerotherapy does not alter the rate of progression to Group 2 or 3 or the rate of development of co-morbidity.

The details of probabilities specific to the arms of Model 1 are provided in *Table 69*.

Alternative analyses were carried out to assess the effect of offering second attempts at sclerotherapy (assuming the same results as primary treatment), higher or lower rates of surgical intervention for those who deteriorate to Group 2 and different ages and discount rates.

Results

The cohort analysis for the Markov model representing the two arms of the trial is shown in *Figure 18*. The model suggests that within 5 years of initial presentation, about 70% of patients have deteriorated to Group 2 or 3, with about 30% having undergone surgical treatment. The use of sclerotherapy makes minimal difference to this prediction.

The base-case analysis of the model (*Table 70*) suggests that sclerotherapy provides an average discounted utility benefit of 0.044 QALY, with a discounted incremental cost of £155.10, giving an ICER of £3531 per QALY.

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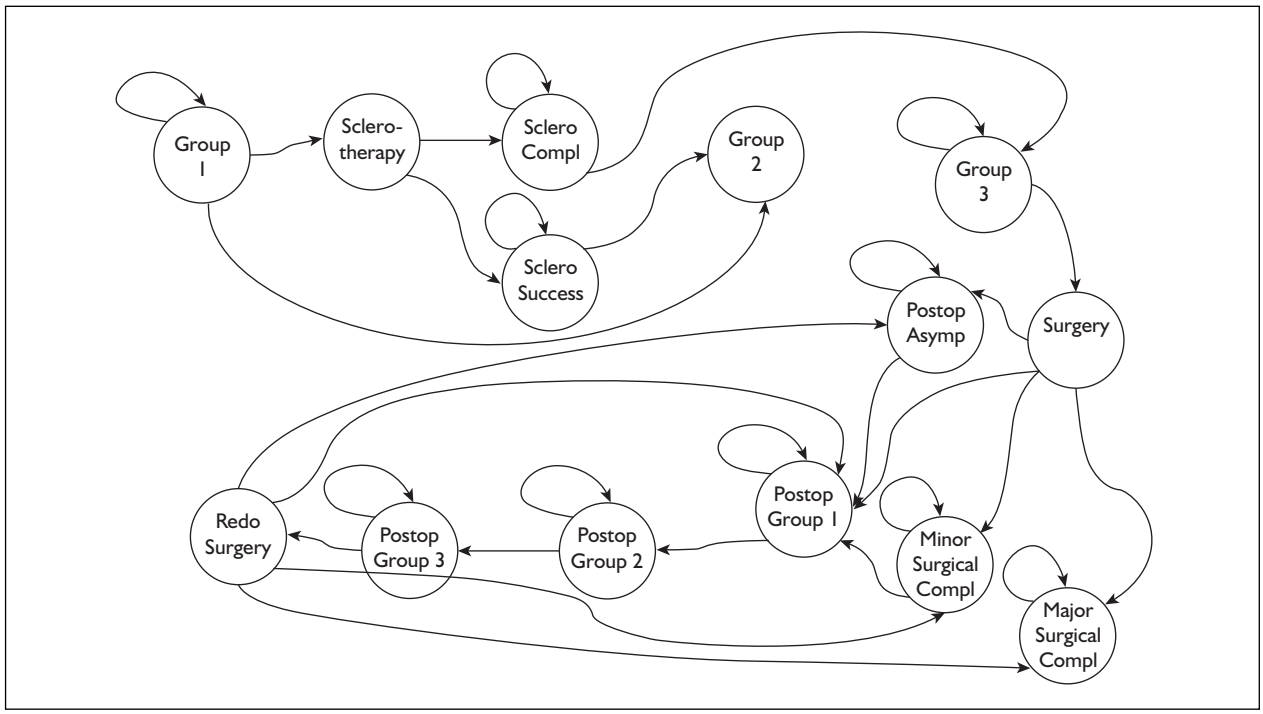

FIGURE 17 *Influence diagram for Model 1. For simplicity, the additional states of co-morbidity and death are not shown. These have incoming branches from all other states.*

TABLE 69 *Probabilities for the base case specific to Model 1*

Description	Value (%)	Comment	Source
Probability of patient in Group 1 having sclerotherapy	0.0	Base case assumes that patients who remain in or return to Group 1 after sclerotherapy will not have further sclerotherapy. Alternative analysis considered a 10% rate of reintervention	Expert opinion
Probability of patient in Group 2 having sclerotherapy	0.0	Model 1 assumes that if patient deteriorates despite sclerotherapy then they would be considered for surgery and not undergo further sclerotherapy	Expert opinion
Probability of patient in Group 2 having surgery	20.0	Rate of surgery if patient deteriorates to Group 2 assumed to be 20% per year with alternative analysis for rates of 0 and 50%	Expert opinion and clinical trial
Probability of patient in Group 3 having surgery	30.0	Higher rate for Model 1 than 2 as patients who present with less severe disease are more likely to seek further treatment if they deteriorate	Expert opinion and clinical trial
Probability of patient in postoperative Group 2 having redo surgery	10.0	Less likely to undertake redo surgery than primary operation	Expert opinion
Probability of patient in postoperative Group 3 having redo surgery	10.0	Less likely to undertake redo surgery than primary operation	Expert opinion
Probability of patient with sclerotherapy complication having surgery	0.0	Set as equivalent to rate of surgery in Group 2	Expert opinion
Probability of being in Group 1 following sclerotherapy	33.0	Based on clinical trial results for those in whom there was no improvement following sclerotherapy	Clinical trial

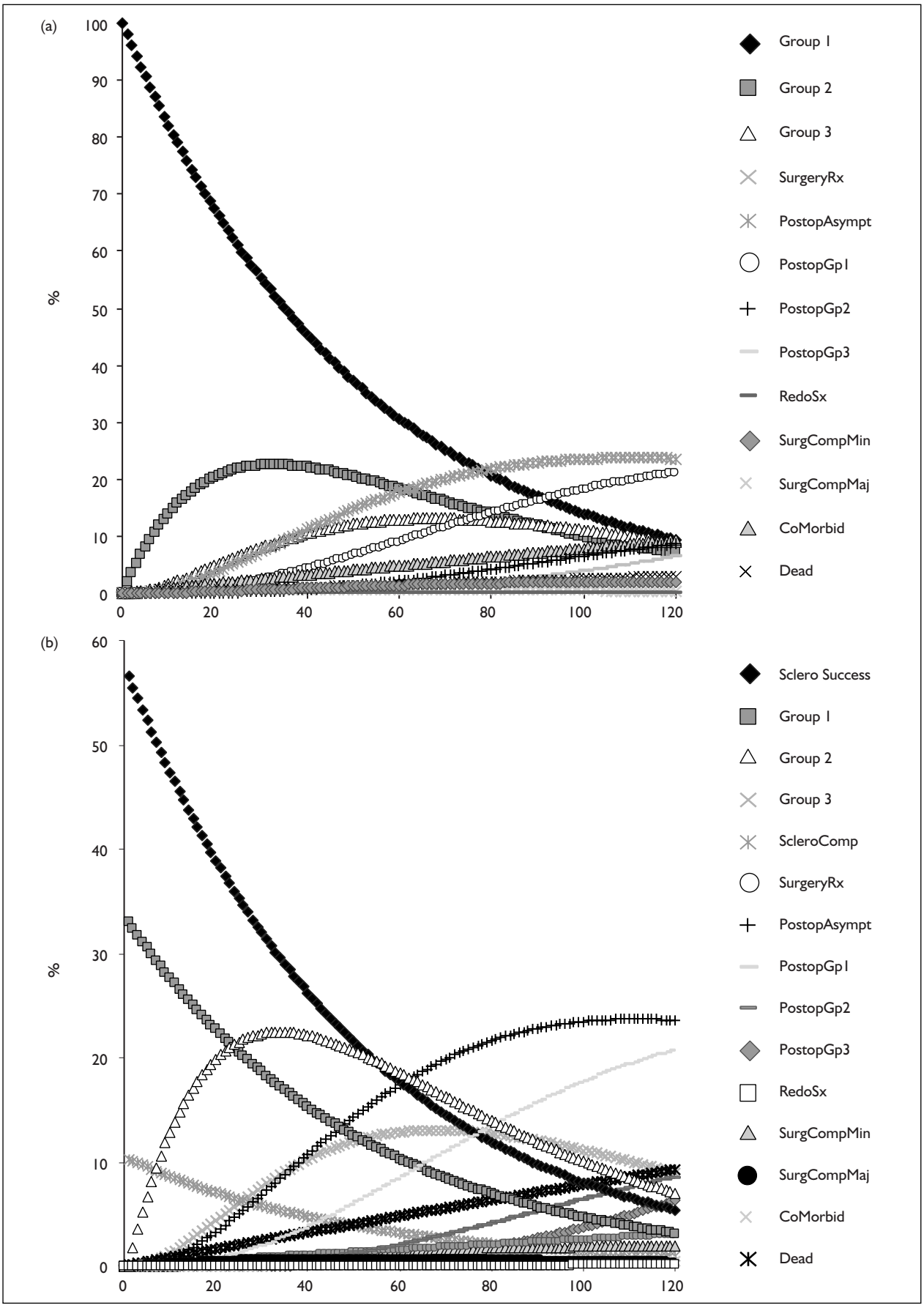

FIGURE 18 *Markov cohort analysis for (a) the conservative arm and (b) the sclerotherapy arm of Model 1*

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TABLE 70 *Base case analysis for Model 1*

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost-effectiveness (£/QALY)	Incremental cost-effectiveness (£/QALY)
Conservative	475.80		6.7453		71	
Sclerotherapy	631.00	155.10	6.7892	0.0439	93	3,531

Dominance report
No strategies were clearly dominated by any other.

TABLE 71 *Sensitivity and alternative analyses for Model 1 (all other variables had an effect of <1%)*

Parameter/scenario	Value	ICER (£/QALY)
Univariate sensitivity analysis		
Utility difference, asymptomatic to Group 3	0.03	10,531
	0.12	2,650
Cost of sclerotherapy (£)	80	1,710
	320	7,172
Probability of no improvement (i.e. remaining in Group 1) after sclerotherapy (%)	20	2,700
	50	5,908
Probability of complication after sclerotherapy (%)	3	2,578
	15	5,640
Rate of progression in absence of reflux (per year) (%)	15	2,901
	25	4,246
Cost of surgery (£)	393	3,585
	1570	3,423
Probability of residual veins (Group 1) after surgery (%)	0	3,542
	20	3,520
Alternative analyses		
Discount rate for costs and utilities (%)	0	3,141
	7	3,930
Annual rate of redo sclerotherapy in Group 1 (%)	0	3,531
	10	3,348
Age at presentation (years)	20	3,491
	60	3,600
Rate of surgery in patients who deteriorate to Group 2 (%)	0	3,499
	50	3,547

Univariate sensitivity analyses were carried out as described above. *Table 71* shows the result of the sensitivity analysis for ICER. The greatest effect on cost-effectiveness was seen with a reduction of utility differences to 0.01 between adjacent clinical states, which increased the overall cost per QALY to an estimated £10,500. Three other variables had an effect on overall incremental cost-effectiveness of >10% (cost of sclerotherapy, probability of successful sclerotherapy and probability of sclerotherapy complication), and a further two had a >1% effect (probability of progression, cost of surgery). All other variables had an effect of <1% over the range used for sensitivity analysis.

Multivariate sensitivity analysis was carried out as described above. The result is shown in *Figure 19*, with the circle representing the 95% confidence boundary and the dotted line representing a £30,000 per QALY threshold. As can be seen, all simulations showed a positive incremental effectiveness and positive incremental cost for sclerotherapy, as compared with conservative

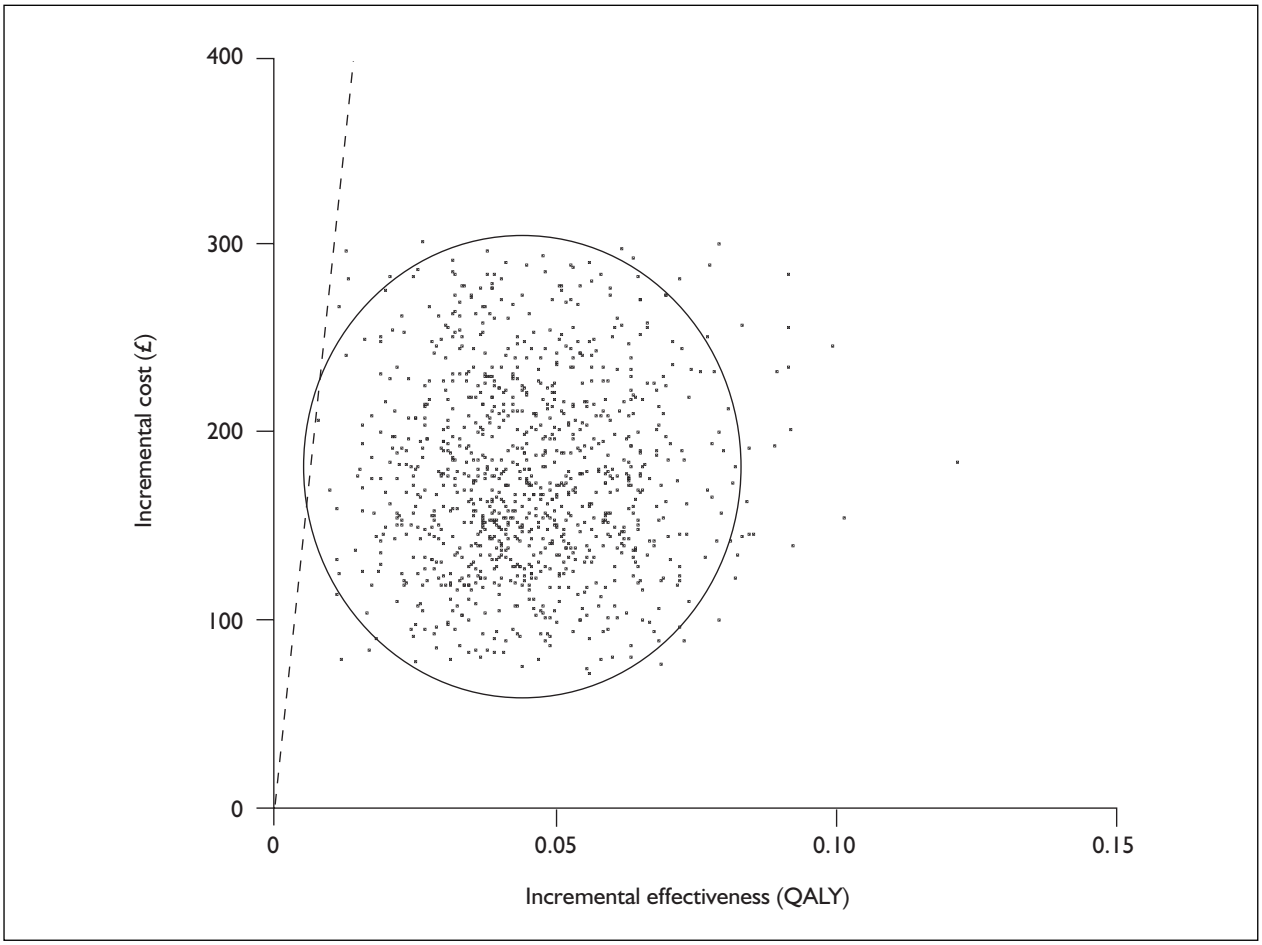

FIGURE 19 *Scatter plot (sclerotherapy versus conservative) of Monte Carlo sensitivity analysis using 1000 simulations. The dashed line represents £30,000/QALY WTP threshold and the circle shows 95% CIs.*

treatment, with the median ICER being £4087 per QALY with an inter-quartile range of £3069–5804 per QALY.

Alternative strategies made little difference to these findings, with only discount rates affecting the estimated cost-effectiveness by >10% (*Table 71*).

Key points

- In patients with minor varicose veins and no reflux, injection sclerotherapy provides a small incremental benefit of about 0.044 QALY (about 16 days of quality-adjusted survival).
- The additional benefit is at an incremental cost of about £155, giving an ICER of about £3500 per QALY.
- The results are robust to univariate and multivariate sensitivity analysis, with all tested parameters providing incremental cost effectiveness ratios well below a willingness-to-pay threshold of £30,000 per QALY.

Model 2

Specific assumptions

The second model represents the scenario that applied to Group 2 patients in whom both surgery and sclerotherapy were possible options. The influence diagram representing the Markov model for this trial is shown in *Figure 20*. Although the clinical trial made a direct comparison between surgery and sclerotherapy, there is a theoretical possibility of conservative treatment in these patients, and this option was therefore considered as a third arm in the model. For the purposes of the model, it was assumed that patients who were initially treated by surgery would not subsequently be offered sclerotherapy, but would be offered redo surgery if they deteriorated to Group 2 or 3, with an uptake rate that approximates to the rates seen in the clinical trial for patients in Group 2 and 3. Details of the base-case probabilities are given in *Table 72*.

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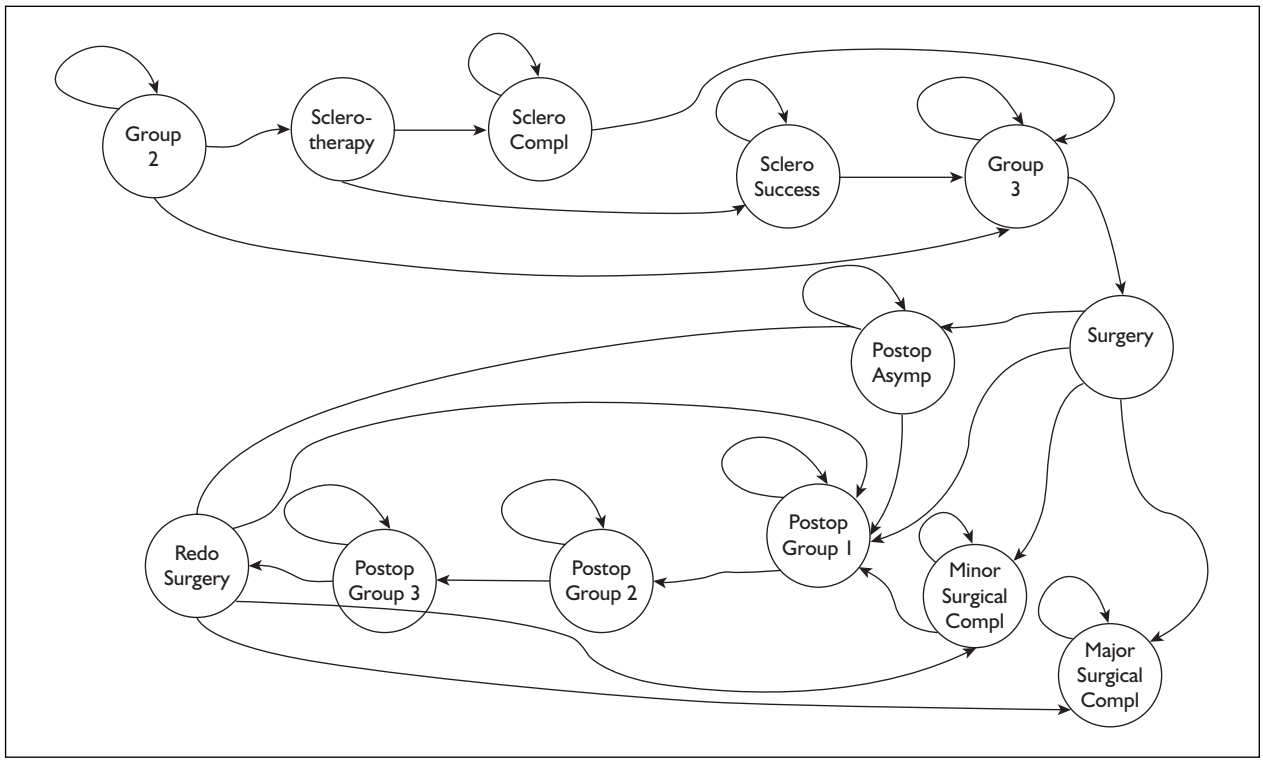

FIGURE 20 *Influence diagram for Model 2. For simplicity, the additional states of co-morbidity and death are not shown. These have incoming branches from all other states.*

TABLE 72 *Probabilities for the base case specific to Model 2*

Description	Value (%)	Comment	Source
Probability of patient in Group 2 having sclerotherapy	0.0	Base case assumes that patients who remain in or return to Group 2 after sclerotherapy will not have further sclerotherapy. Alternative analysis will include the possibility of second and subsequent attempts at sclerotherapy	Expert opinion
Probability of patient in Group 2 having surgery	0.0	Base case assumes that those treated by sclerotherapy will only have surgery if they deteriorate to Group 3. Alternative analysis includes possibility of crossover to surgery	Expert opinion and clinical trial
Probability of patient in Group 3 having surgery	20.0	Lower rate for Model 2 than 1 as it is assumed that patients who present with more severe disease are less likely to seek further treatment if they deteriorate	Expert opinion and clinical trial
Probability of patient in postoperative Group 2 having redo surgery	5.0	For those in Group 2 who have undergone primary surgery it is assumed that some would undergo redo surgery if they deteriorate to Group 2, but at a lower rate than those reaching Group 3	Expert opinion
Probability of patient in postoperative Group 3 having redo surgery	10.0	Less likely to undertake redo surgery than primary operation	Literature review and expert opinion
Probability of patient with sclerotherapy complication having surgery	0.0	Set as equivalent to rate of surgery in Group 2	Expert opinion
Probability of being in Group 2 following sclerotherapy	36.0	Based on clinical trial results for those in whom there was no improvement following sclerotherapy	Clinical trial

For those patients who were initially treated by sclerotherapy, it was assumed that they would not be offered further sclerotherapy, but that they would be offered surgery if they deteriorated to Group 3, and redo surgery at a similar rate of those patients in the surgery arm. Those patients who initially underwent conservative treatment would not be offered either sclerotherapy or surgery while they remain in Group 2, but would be offered surgery with uptake at a similar rate to the above if they deteriorated to Group 3. In the clinical trial there was a fairly high rate of crossover between the arms of the trial, with many patients who were randomised to sclerotherapy requesting subsequent surgery. However, the situation of a clinical trial is an artificial one and secondary analysis was carried out to consider the possibility of a lower rate of uptake of surgery in those patients undergoing conservative treatment or sclerotherapy who deteriorate to Group 3.

Alternative analyses were also carried out to assess the effect of offering second attempts at sclerotherapy (assuming the same results as primary treatment), the possibility of surgical intervention or redo sclerotherapy for some patients who remain in Group 2, different ages and discount rates.

Results

Figure 21 shows the outcome for the cohort analysis in each of the treatment arms of the model. The analysis suggests that at 5 years from the start of the model approximately 38% of those treated conservatively are in Group 3 and 34% have undergone surgery. The figures for sclerotherapy are similar, with a slight reduction in the rate of surgery of <1%. For surgical treatment approximately 28% are asymptomatic, 35% in Group 1 5 years after the initial treatment and 4.0% have undergone redo surgery. The total proportion of patients in Group 2 or 3 at 5 years, either with or without surgery, is 27.3% for surgery, 49.5% for sclerotherapy and 61.1% for conservative treatment. By 10 years, approximately 67% of the conservative and sclerotherapy arms of the model have undergone surgery and 19% of the surgical arm have undergone redo surgery.

Table 73 provides the base-case analysis of the cost-effectiveness modelling. Compared with conservative treatment, sclerotherapy provides an incremental benefit in discounted effectiveness of 0.046 QALY, at a discounted incremental cost of £155.40, providing an ICER of £3388 per QALY. Compared with conservative treatment, surgical treatment provides a discounted benefit in effectiveness of 0.214 QALY, at a discounted incremental cost of £446.60, providing an ICER of £2083 per QALY. Surgical treatment shows extended dominance over sclerotherapy in that, compared with expenditure on sclerotherapy, a greater benefit could be provided by a blend of conservative and surgical treatment.

TABLE 73 *Base-case analysis for Model 2*

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALY)	Incremental effectiveness (QALY)	C/E (£/QALY)	Incremental C/E (£/QALY)
Conservative	473.20		6.589		72	
Sclerotherapy	628.60	155.40	6.635	0.046	95	3388
Surgery	919.80	291.20	6.803	0.169	135	1728
All options referenced to a common baseline						
Conservative	473.20		6.589		72	
Sclerotherapy	628.60	155.40	6.635	0.046	95	
Surgery	919.80	446.60	6.803	0.214	135	
Without dominated options (simple or extended)						
Conservative	473.20		6.589		72	
Surgery	919.80	446.60	6.803	0.214	135	2083

Dominance report
No strategies were clearly dominated by any other

Extended dominance report
The strategy 'Sclerotherapy' is dominated by a blend of 'Conservative' and 'Surgery', with a coefficient of inequity between 0.652 and 0.786.

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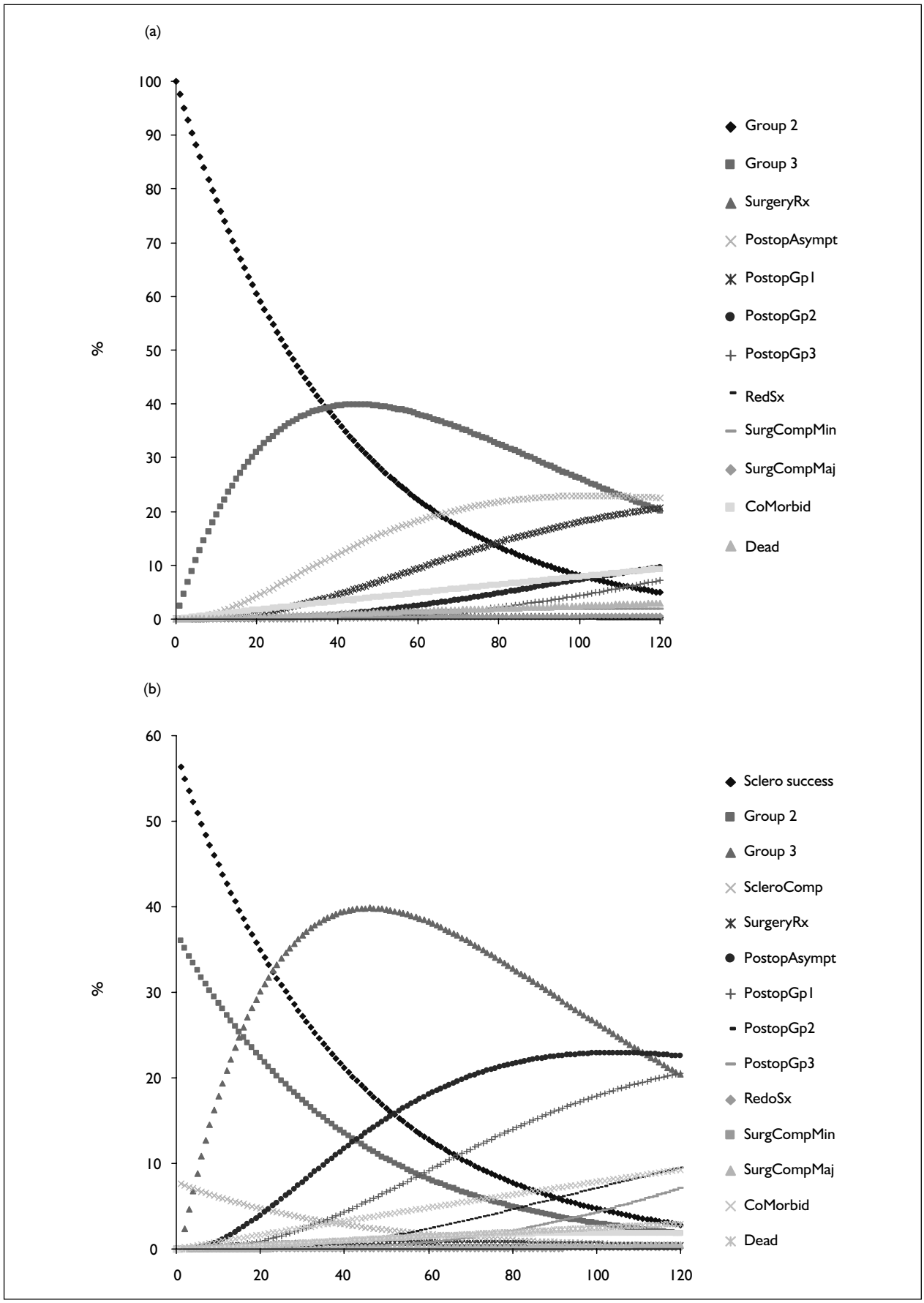

FIGURE 21 *Markov cohort analysis for (a) the conservative arm, (b) the sclerotherapy arm and (c) the surgery arm of Model 2*

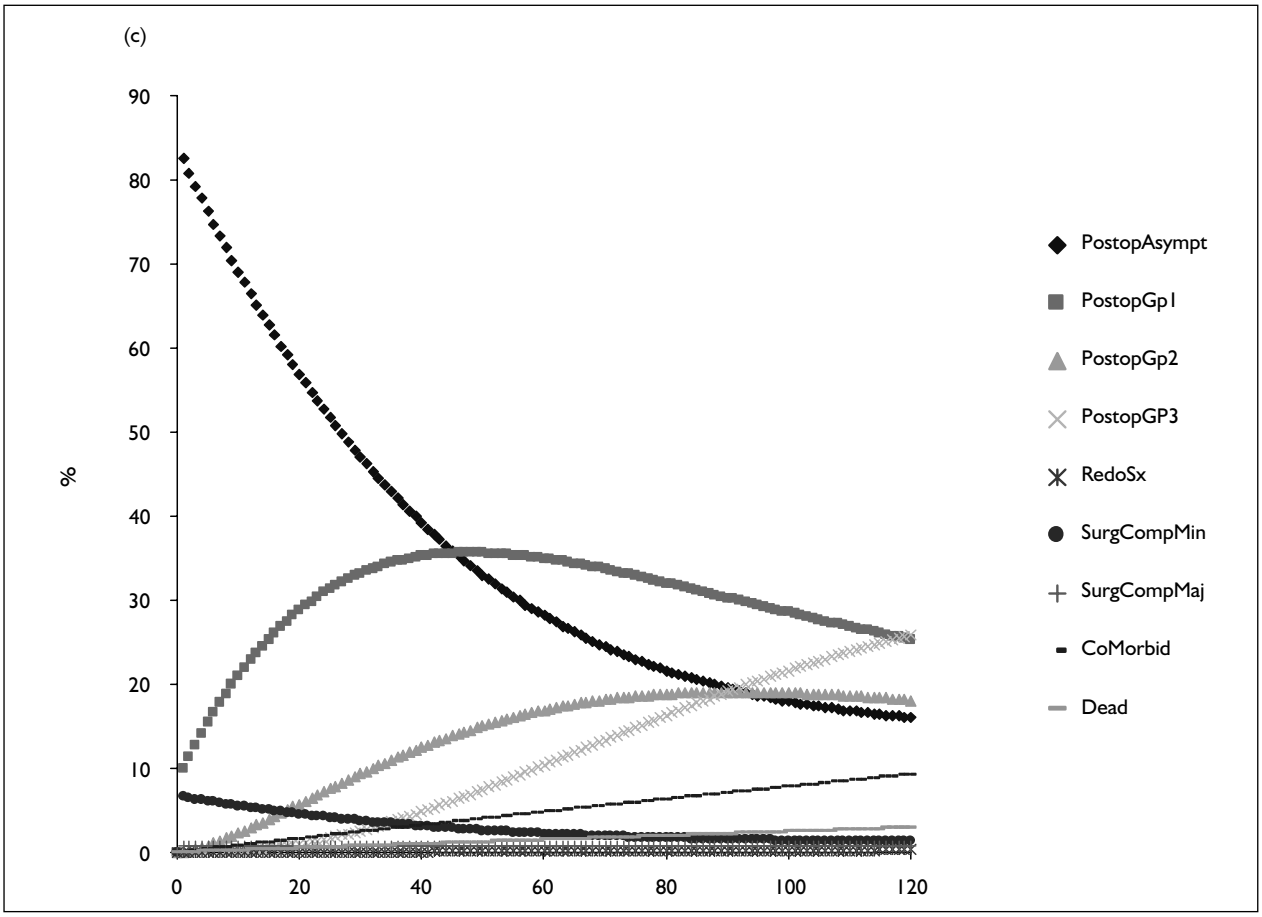

FIGURE 21 (cont'd) *Markov cohort analysis for (a) the conservative arm, (b) the sclerotherapy arm and (c) the surgery arm of Model 2*

One-way sensitivity analysis was carried out on the parameters listed in *Tables 66–68*, and the results are shown in *Table 74* in terms of the differences in incremental cost-effectiveness of surgery and sclerotherapy compared with conservative treatment. In the majority of situations surgical treatment provides improved outcomes compared with conservative treatment, with a lower ICER than sclerotherapy, thus showing extended dominance. The exceptions to this are where the cost of sclerotherapy is <£100 or the cost of surgery is >£1250. Under these circumstances, surgery continues to provide the greatest benefit but at a higher ICER than sclerotherapy. Within the full range of one-way sensitivity analysis, the highest cost per QALY was under £6000 for surgical treatment. For sclerotherapy the highest cost per QALY was just over £10,000.

Multivariate sensitivity analysis was carried out through a Monte Carlo simulation, as described for Model 1. The scatter diagrams representing the results of this for 1000 simulations are given in *Figure 22* for the comparisons of conservative treatment against sclerotherapy, conservative treatment against surgery and sclerotherapy against surgery. In all cases, surgical treatment provides the greatest benefit in outcome at the highest cost, with the median ICER compared with conservative treatment being £2363 per QALY with an inter-quartile range of £1805–3116 per QALY, and all observations well within the threshold of £30,000 per QALY.

In the alternative strategies (*Table 74*), a higher rate of surgical intervention for those in Group 2 resulted in surgery showing dominance over sclerotherapy (having lower cost with better outcomes) if the intervention rate exceeded 15%. Other alternative strategies did not alter the overall results, with a maximum increase of £3900 in the cost per QALY for surgical treatment.

Key points

- In patients with moderate varicose veins, injection sclerotherapy and surgical treatment provide an incremental benefit of 0.046 and 0.214 QALY, respectively.

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TABLE 74 *Sensitivity and alternative analyses for Model 2: ICER for sclerotherapy (against conservative treatment) and surgery (against sclerotherapy)*

		ICER (£/QALY)	
Parameter/scenario	**Value**	**Surgery**	**Sclerotherapy**
Univariate sensitivity analysis			
Cost of sclerotherapy (£)	80	2202	1,644
	320	779	6,877[a]
Cost of surgery (£)	393	416	3,437[a]
	1570	4356	3,290
Utility difference, asymptomatic to Group 3	0.03	6029	10,112[a]
	0.12	1274	2,543[a]
Probability of no improvement (i.e. remaining in Group 2) after sclerotherapy (%)	20	1884	2,599[a]
	50	1611	4,615[a]
Difference in progression rate for reflux vs no reflux (%)	0	2031	2,805[a]
	10	1535	3,987[a]
Probability of complication after sclerotherapy (%)	3	1770	3,116[a]
	15	1664	3,942[a]
Rate of progression in absence of reflux (per year) (%)	15	1525	2,851[a]
	25	2020	3,982[a]
Probability of residual veins (postoperative Group 1) after surgery (%)	0	1562	3,398[a]
	20	1925	3,378[a]
Probability of a major complication after surgery (%)	0.2	1686	3,391[a]
	2	1816	3,384[a]
Alternative analyses			
Rate of surgery for patients in Group 2 (per year) (%)	0	1728	3,388[a]
	50	1923	Dominated
Probability of Group 3 having surgery (%)	0	2334	3,292[a]
	50	1531	3,433[a]
Discount rate for costs and utilities (%)	0	1246	3,082[a]
	7	2207	3,695[a]
Age at presentation (years)	20	1681	3,358[a]
	60	1812	3,440[a]
Probability of Group 2 having redo sclerotherapy (%)	0	1728	3,388[a]
	10	1682	3,409[a]
Probability of postoperative Group 2 having redo surgery (%)	0	1615	3,390[a]
	10	1818	3,387[a]

[a] Demonstrates extended dominance.

- The additional benefit is at an incremental cost of £155.40 for sclerotherapy and £446.60 for surgery, giving ICERs of £3388 and £2083 per QALY, respectively.
- Surgical treatment demonstrates extended dominance over sclerotherapy, having a better ICER than conservative treatment.
- The results are robust to univariate and multivariate sensitivity analysis, with all tested parameters providing ICERs well below a WTP threshold of £30,000 per QALY.

Model 3

The third model represents the situation for the largest group of patients in the clinical trial who were initially in Group 3, with the choice being between conservative management and surgery. The influence diagram representing the Markov model for this trial is shown in *Figure 23*. The assumption is made that sclerotherapy would not be available to these patients. In the base case, it is assumed that patients in the conservative arm

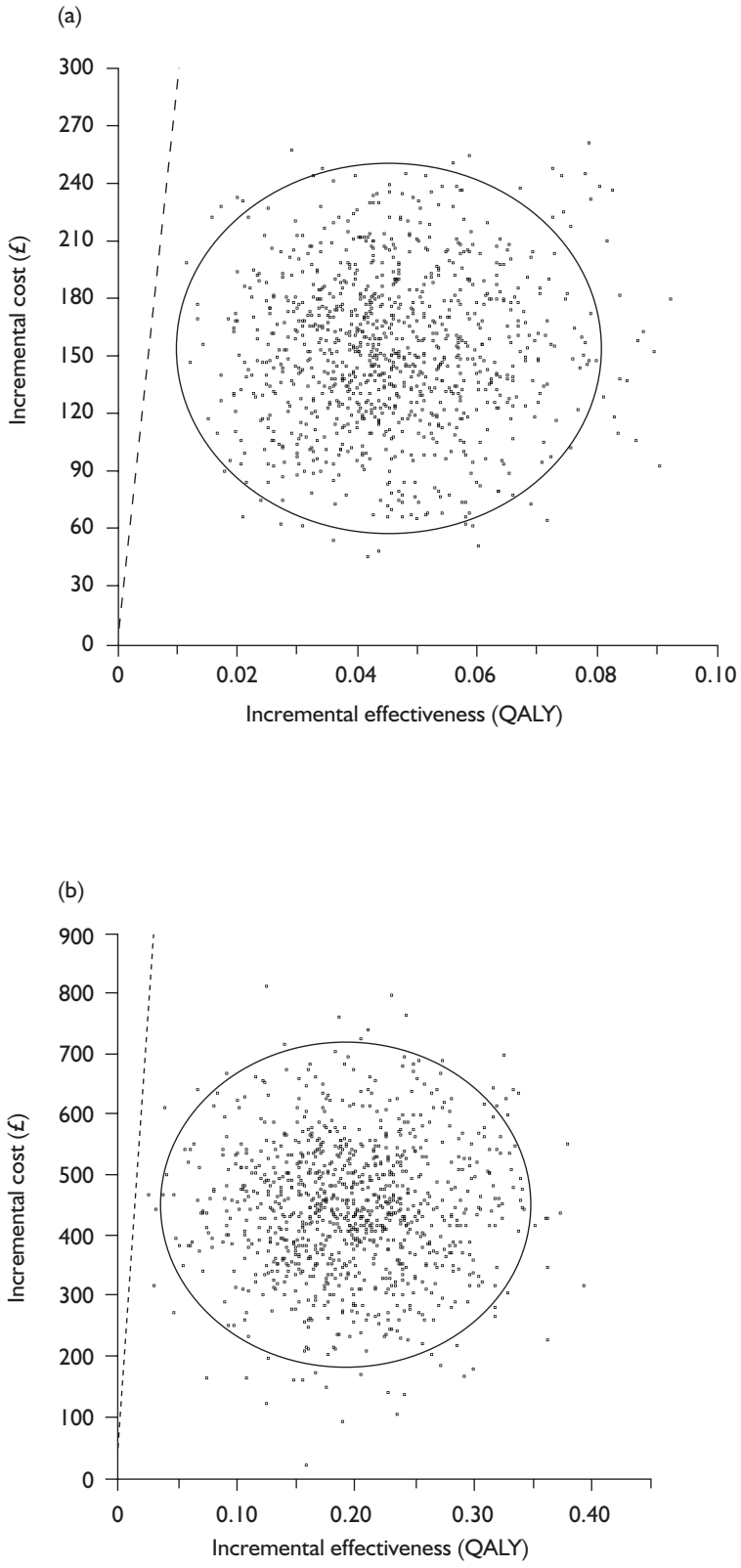

FIGURE 22 *Scatter plot of Monte Carlo sensitivity analysis using 1000 simulations for (a) sclerotherapy vs conservative treatment, (b) surgery vs conservative treatment and (c) surgery vs sclerotherapy. The dashed line represents £30,000/QALY WTP threshold and the circle shows 95% CIs.*

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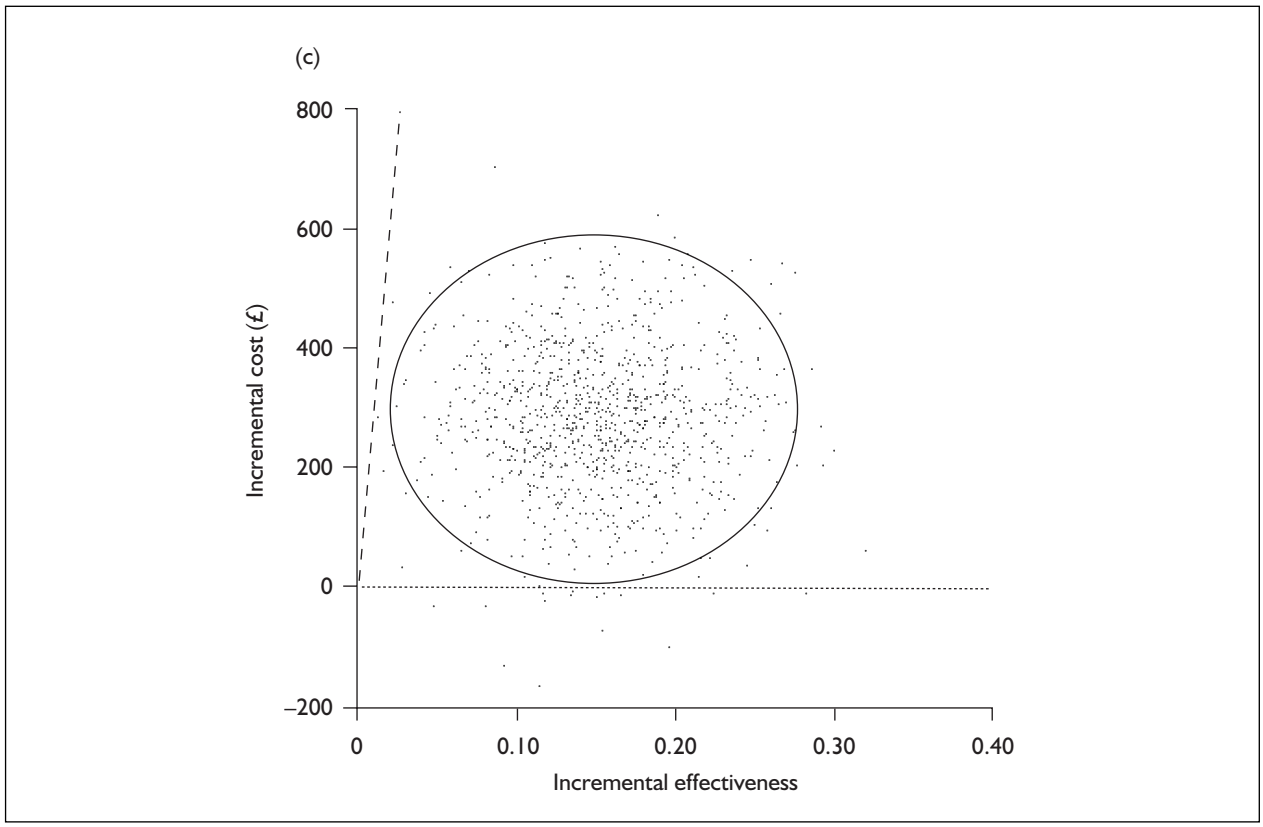

FIGURE 22 (cont'd) *Scatter plot of Monte Carlo sensitivity analysis using 1000 simulations for (a) sclerotherapy vs conservative treatment, (b) surgery vs conservative treatment and (c) surgery vs sclerotherapy. The dashed line represents £30,000/QALY WTP threshold and the circle shows 95% CIs.*

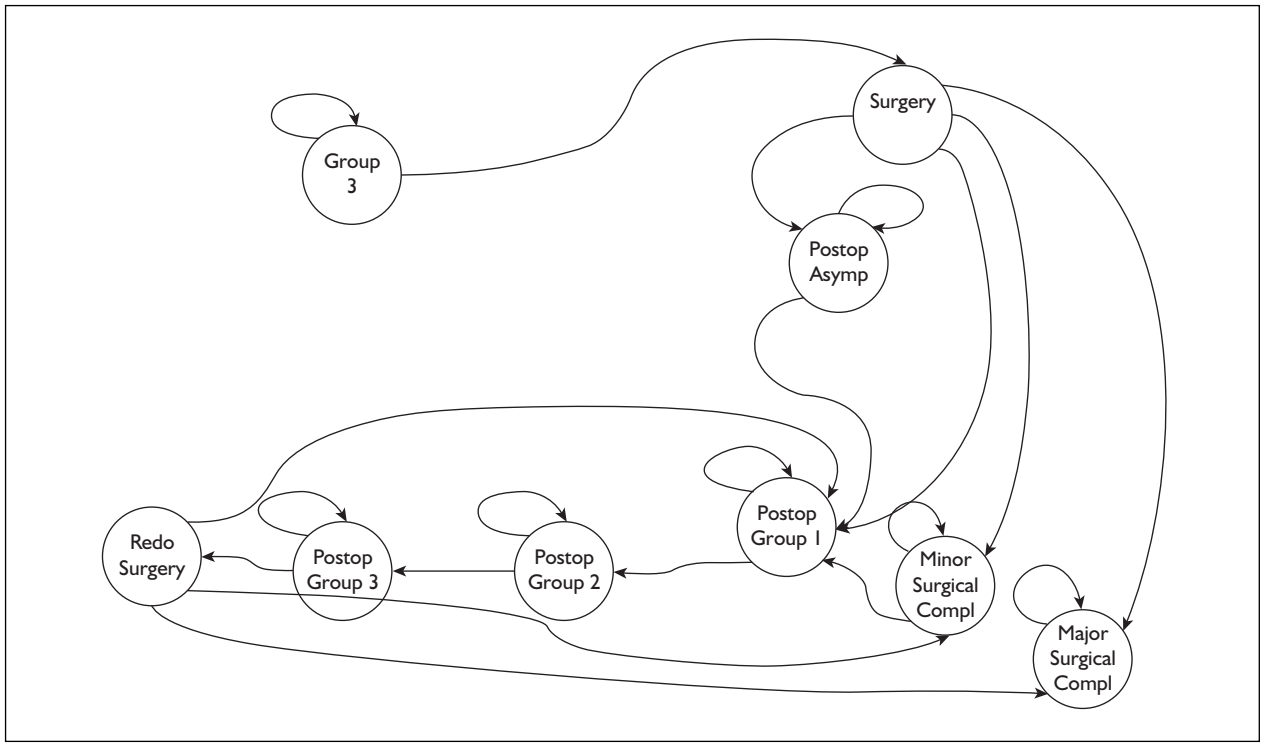

FIGURE 23 *Influence diagram for Model 3. For simplicity, the additional states of co-morbidity and death are not shown. These have incoming branches from all other states.*

TABLE 75 *Probabilities specific to Model 3*

Description	Value (%)	Comment	Source
Probability of patient in Group 3 having surgery	0.0	Base case in Model 3 assumes those with initial conservative treatment are never offered surgery. Alternative analysis considers possibility of offering surgery, at a rate equivalent to crossover rate in clinical trial	Expert opinion and clinical trial
Probability of patient in postoperative Group 2 having redo surgery	0.0	It is assumed that patients would not present for redo surgery unless they were at least as bad as when they presented for primary surgery	Expert opinion
Probability of patient in postoperative Group 3 having redo surgery	10.0	Rate of redo surgery for Group 3 as in Model 2	Literature review and expert opinion

TABLE 76 *Base-case cost-effectiveness analysis for Model 3*

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALY)	Incremental effectiveness (QALY)	C/E (£/QALY)	Incremental C/E (£/QALY)
Conservative	0.00		6.341	0		
Surgery	879.80	879.80	6.795	0.453	129	1,941

Dominance report
No strategies were clearly dominated by any other

Extended dominance report
No strategies were eliminated by extended dominance

do not have surgical treatment available and that retreatment of patients undergoing surgery would only be available to those patients in Group 3 at a similar rate to that described above (*Table 75*).

Secondary analyses were carried out to consider a number of alternative strategies. The first is the use of a 2-year time horizon, in order to assess the validity of the model through considering a similar horizon to the cost-effectiveness analysis in Chapter 5. A second alternative analysis considered the effect of a waiting list, comparing immediate surgery with surgical intervention after a delay of 6 months. A further simulation was carried out to consider the possibility of a higher rate of development of co-morbidity amongst those patients in Group 3 either prior to or following surgical intervention. Other secondary analyses considered higher rates of surgical intervention in those undergoing initial conservative treatment and the effects of age and discount rates.

Results

The Markov cohort analysis for the operated and unoperated cohorts in the base-case scenario are shown in *Figure 24*. In the conservative arm, apart from those patients developing mortality or co-morbidity, all patients are assumed to remain indefinitely in Group 3. In those undergoing initial surgery, by 2 years 48% have developed some recurrent varicose veins, with 9% having recurrent reflux (Groups 2 or 3), and by 5 years 73% have some recurrence, with 31% having recurrent reflux. Overall, 13% of patients have redo surgery within 10 years.

The result of the cost-effectiveness analysis for the base case is given in *Table 76*. Surgical intervention provides a discounted benefit in effectiveness of 0.453 QALY, at a discounted incremental cost of £879.80, giving an ICER of £1941 per QALY.

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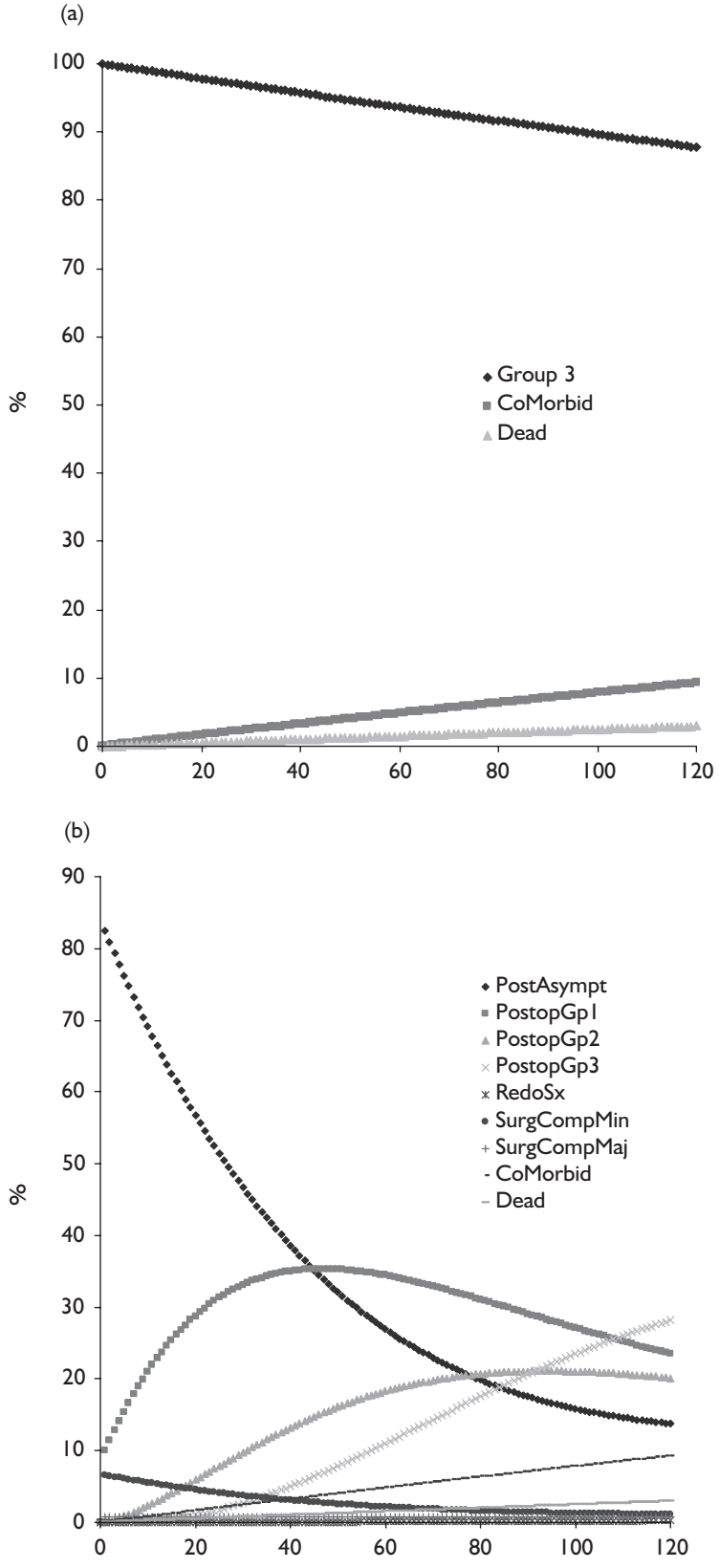

FIGURE 24 *Markov cohort analysis for (a) the conservative arm and (b) the surgery arm of Model 3*

TABLE 77 *Sensitivity and alternative analyses for Model 3*

Parameter/scenario	Value	ICER (£/QALY)
Univariate sensitivity analysis		
Utility difference, asymptomatic to Group 3	0.03	6480
	0.12	1437
Cost of surgery (£)	393	993
	1570	3841
Rate of progression in absence of reflux (per year) (%)	15	1698
	25	2228
Probability of surgery leaving residual veins (postoperative Group 1) (%)	0	1842
	20	2051
Cost of having a major surgical complication (per month) (£)	0	1941
	100	2114
Probability of a major complication after surgery (%)	0.2	1909
	2	2008
Difference in progression rate for reflux vs no reflux (%)	0	1907
	10	1967
Probability of residual veins (postoperative Group 1) after surgery (%)	0	1842
	20	2051
Probability of a minor complication after surgery (%)	2	1910
	10	1965
Alternative analyses		
Probability of Group 3 having surgery (%)	0	2334
	50	1531
Discount rate for costs and utilities (%)	0	1246
	7	2207
Probability of postoperative Group 3 having redo surgery (%)	0	1837
	20	2004
Higher probability of co-morbidity in Group 3 (%)	2	1864
Age at presentation (years)	20	1918
	60	1982
Delay in surgery (months)	6	1948
Shorter time horizon (years)	2	5903

Univariate sensitivity analysis was carried out on each of the variables listed in *Tables 66–68*, and the results are shown in *Table 77*. In all analyses, surgical treatment provided the greatest outcome benefit at the highest cost, with a maximum incremental cost-effectiveness of £6480 per QALY where the utility difference between adjacent states is reduced to 0.01.

Multivariate sensitivity analysis was carried out using a Monte Carlo simulation as described above, and the results are shown in the form of a scatter plot of ICERs in *Figure 25*. Once again it can be seen that surgical treatment provides improved outcomes at increased cost, with the median ICER being £1838 per QALY with an inter-quartile range of £1432–2392 per QALY, and all observations well within the WTP threshold of £30,000 per QALY.

The results for the alternative strategies are given in *Table 77* and for the strategies of delayed treatment and crossover treatments the Markov cohort analysis is shown in *Figure 26*. A reduction in time horizon to 24 months results in an ICER of £5903 per QALY. Alternative strategies involving delay in surgery or the possibility of surgery in those treated initially by conservative measures result in intermediate cost and outcomes. In both cases immediate surgery demonstrates extended dominance with better outcomes for a lower ICER. Age at presentation has little effect on cost-effectiveness.

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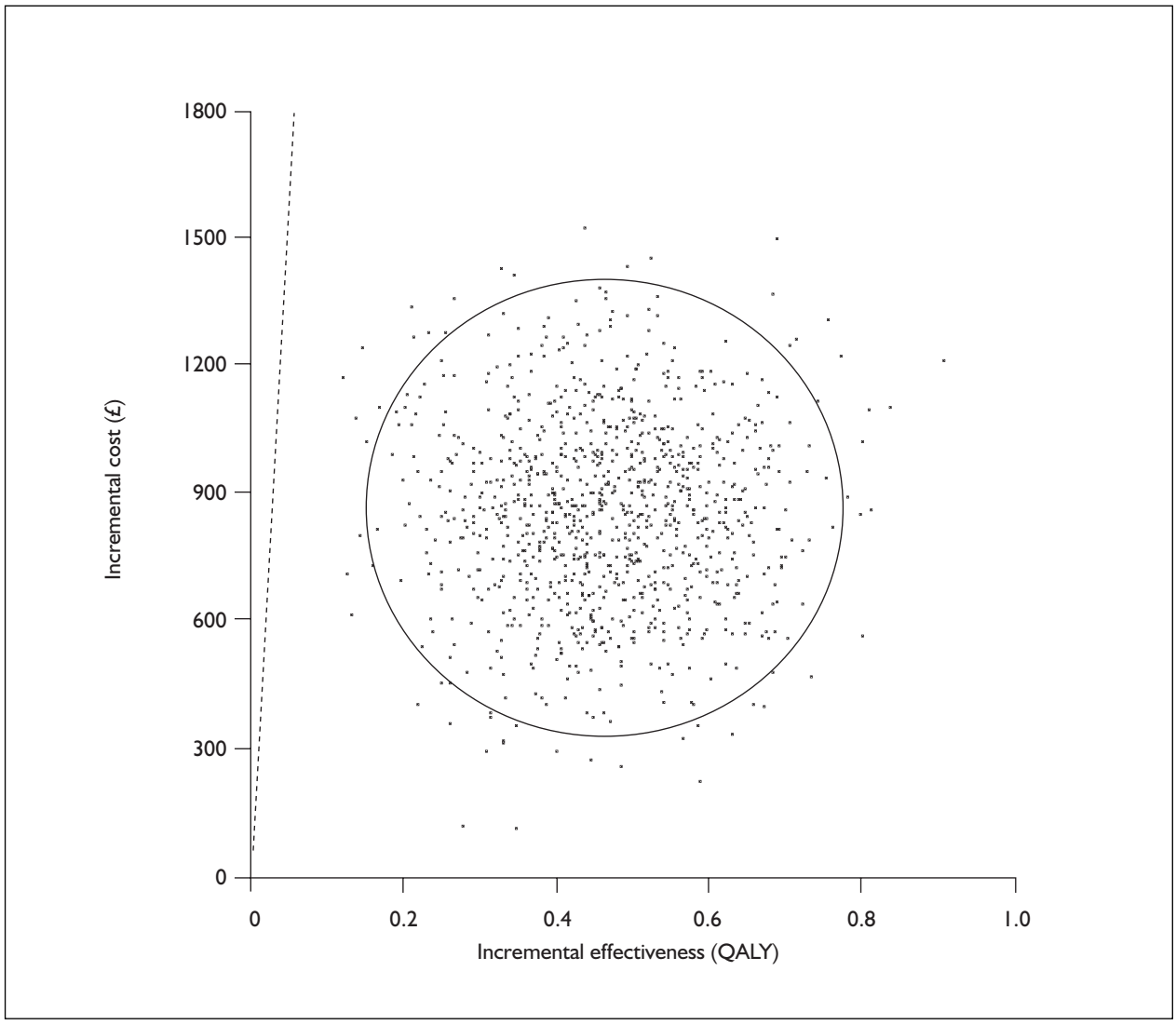

FIGURE 25 *Scatter plot (surgery vs conservative) of Monte Carlo sensitivity analysis using 1000 simulations for Model 3. The dashed line represents £30,000/QALY WTP threshold and the circle shows 95% CIs.*

Key points

- For patients in Group 3, surgery produces an estimated benefit of 0.453 QALY compared with conservative treatment.
- This benefit is provided at a discounted incremental cost of £879.80, giving an ICER of £1941 per QALY.
- Where surgical treatment is delayed through waiting lists or initial conservative treatment followed by surgical treatment, the benefit of surgery is reduced and early surgery shows extended dominance over these options.
- All these findings are robust across a range of different assumptions about management policies and through a series of one-way and multivariate sensitivity analyses covering the areas of uncertainty within the estimated parameters.
- The effect of a possible reduction in major morbidity (e.g. DVT and ulceration) following successful treatment of uncomplicated varicose veins is to reduce the ICER to £1864 per QALY.
- The results of the modelling correspond closely with the results of the economic analysis based on the clinical trial described in Chapter 5.

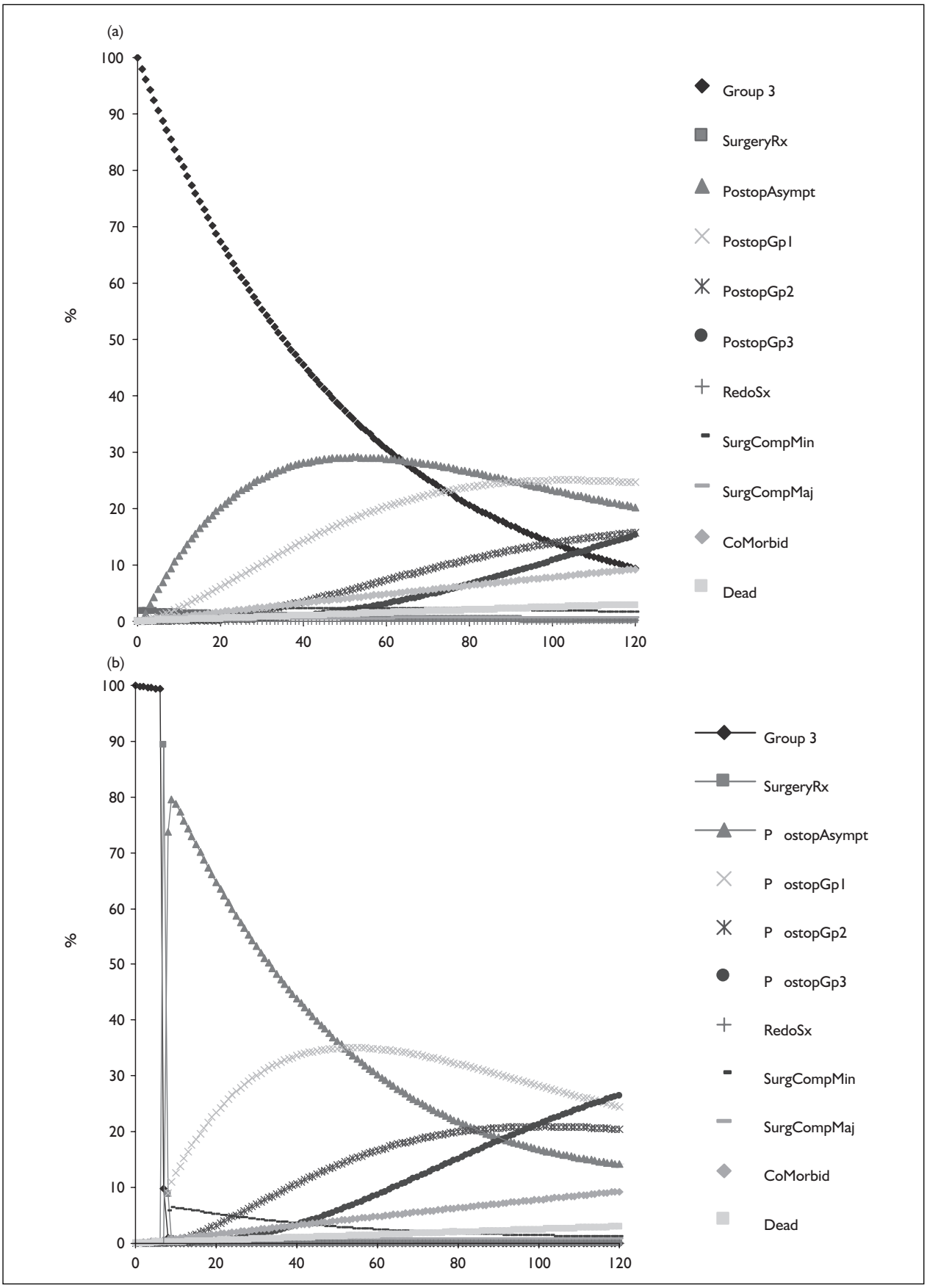

FIGURE 26 *Markov cohort analysis for alternative models with (a) crossover to surgical treatment and (b) 6 months delay in surgery for Model 3*

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Chapter 7
Discussion and conclusions

Introduction

Varicose veins are a common condition, and many patients seek treatment for symptomatic relief or the alleviation of cosmetic concerns. Over 40,000 surgical procedures are carried out each year in England and Wales,[5] with an unknown additional number of patients undergoing sclerotherapy. The most commonly employed methods of surgical treatment and injection sclerotherapy have changed little in many years, and are an established part of clinical practice. However, the cost-effectiveness of these treatments has not been fully assessed in the past, and the pressures on waiting lists and healthcare resources have led to moves in some areas to restrict their availability. This has resulted in geographical variations in the availability of and indications for these procedures.[19]

The fact that these procedures are well established and widely used creates some difficulty in carrying out new research work in this area. Those patients who are referred to secondary care for assessment form a selected population who are seeking active treatment, and may therefore be less inclined to participate in RCTs. In addition, they may not be representative of the wider population of patients who might seek such treatments if they were to become more easily available. A further problem is the importance of evaluating the recurrence rate following treatment, which is difficult because patients with varicose veins are often reluctant to attend for repeated follow-up assessments.

This study set out to evaluate the cost-effectiveness of the common interventions for treatment of varicose veins. In recognition of the potential difficulties referred to above, the study used a range of approaches, including systematic literature review, RCTs, an observational study and economic analysis and modelling.

Classification

There is a need to define those groups of patients most likely to benefit from particular forms of intervention. A suitable classification system should enable particular subgroups of patients with varicose veins to be consistently identified both for the purposes of research and for clinical management. Existing classification systems have proved to be of limited value in identifying subgroups of patients with uncomplicated varicose veins for these purposes.

The review of the literature (Chapter 2) shows that there is little information of high quality about the progression of varicose veins, and recurrence following treatment. Part of this is due to the lack of a uniform classification system for uncomplicated varicose veins. Without such a classification, it is difficult to gauge or report on the extent, rate of recurrence or progression of disease. The classification described in Chapter 3 has the potential to allow more detailed assessment and comparison of the extent of uncomplicated varicose veins. In order to be considered valid, it should respond as expected to changes in clinical state, be responsive to the results of treatment, relate to clinical outcomes such as symptomatic change, patient satisfaction and HRQoL and give a reasonable spread allowing sensitivity to progression of disease.

The anatomical classification that was devised for the purposes of the study (Chapter 3) met many of the criteria for face validity, in that it showed the expected differences between patient groups based on the treatments undertaken and correlated with other clinical factors, such as the presence of reflux, the type of treatment used and some symptomatic and HRQoL measures. It also appeared to be sensitive, with a spread of patients across the different anatomical categories. Although some of the criteria for the classification were subjective, with vein size and extent being estimated visually, this was a pragmatic approach to developing a classification that could be applied routinely without special equipment. Its suitability for use in a clinical setting was supported by the close agreement between the clinicians who participated in the validation exercise.

Clinical trial recruitment

The trial design included an observational study alongside the RCTs. This has a number of

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advantages. It allows an estimate of the extent to which the randomised population differs from the general population of patients referred with the condition. It also allows more accurate estimates of the incidence of complications and provides additional data that can be used in a sensitivity analysis for economic modelling.

Although there are a number of new and novel treatments for varicose veins, most patients in the UK are either treated conservatively (including compression hosiery and general advice about lifestyle), by injection sclerotherapy or by surgery (most commonly ligation and stripping of the LSV and multiple phlebectomies). These were, therefore, the treatments chosen for the clinical trial.

The referral and recruitment rates were lower than was predicted when the protocol was being developed, particularly for those patients with minor varicose veins. This may reflect a change in referral practice, in that a number of commissioners had recently developed guidelines suggesting that patients with minor varicose veins should not be referred to hospital for treatment, with some going as far as to suggest that only those with significant skin changes should be referred.[19] Although such guidance had not been specifically issued in the districts participating in the trial, such documents had been issued in neighbouring districts and publicity on the importance of 'demand management' as a means of controlling waiting lists may have had a knock-on effect, particularly with respect to patients with less extensive varicose veins.

One noticeable feature of the recruitment was the considerable difference in recruitment rates to the RCTs between the two centres that were participating in the trial. There are a number of possible reasons for this. There were some differences in demographics and patient population between the two centres. There were also differences in the arrangements for carrying out the trial. In Exeter, recruitment was carried out in normal outpatient clinics, whereas in Sheffield, special research clinics were established, run by a doctor and a nurse specifically involved in the project. The latter may have resulted in the considerably higher recruitment rate, although it is notable that there is a significant proportion of patients who, having initially agreed to participate, subsequently declined their allocated treatment or were dissatisfied and elected to have surgery or sclerotherapy.

There were a number of protocol violations, which may reflect the fairly complex design of the trial, with a number of different recruitment arms and a large number of clinicians participating in recruitment. However, the majority of violations were relatively minor, particularly relating to the recording of BMI, and probably do not have a significant effect on the results of the trial.

The patient population is similar to that seen in other studies of varicose veins in the UK, with similar age and gender mix.[107,108] The majority of patients referred for treatment report symptoms from their varicose veins, particularly aching, heaviness, itching and cosmetic concerns. It is of note that there is little correlation between the anatomical extent of varicose veins and the incidence of specific symptoms. Previous work[7] has suggested that such symptoms may be common in the general population, and may not be caused by the varicose veins. However, the fact that the majority of these symptoms improved following intervention suggest that this is not the case. It is likely, however, that the severity of reported symptoms is a major determinant of referral from primary to secondary care. The higher incidence of symptoms amongst those with anatomically less severe veins may reflect selection at the point of referral, in that patients with very extensive veins are more likely to be referred with fewer symptoms. A number of patients were referred with extensive varicose veins who reported no symptoms.

The effect of selective referral may also explain the findings in respect of the HRQoL measures, in that those in the groups with apparently more severe varicose veins on anatomical measures did not have a lower HRQoL at baseline on any of these measures. This is likely to reflect the fact that only those who are most troubled by their veins are referred at an early stage of the condition.

There were no significant differences between either the demographic characteristics or the outcomes of those patients who consented to randomisation compared with those who declined randomisation and elected to have a specific treatment.

Group 1 trial

The Group 1 trial dealt with patients who had minor varicose veins, not felt to be appropriate for surgical intervention. In such cases, the usual conventional alternatives are sclerotherapy or conservative management. The trial suggested that patients are more likely to be satisfied with the results of sclerotherapy at 1 year, with better

cosmetic results and fewer symptoms. However, the numbers in this trial were small and represented a highly selected population, in that most patients with such minor varicose veins are not referred to secondary care for treatment. Skin staining was identified by a significant proportion of patients undergoing sclerotherapy, but on direct questioning the majority of patients did not consider this a problem or complication and were satisfied with the results of treatment despite their staining.

Group 2 trial

The Group 2 trial compared sclerotherapy and surgical treatment in those who were eligible for either treatment. The result suggested that both treatments produced satisfactory outcomes at 1 year. Surgery produced better anatomical results and significant benefit in some HRQoL measures, but did not produce significantly greater symptomatic improvement. This may represent a Type 2 error, owing to the relatively small number of patients recruited and the incomplete follow-up. One important issue in comparing surgery and sclerotherapy is the question of recurrence rates following the two treatments. The literature review (Chapter 2) suggests that recurrence rates after sclerotherapy are significantly higher than those following surgical treatment. The power and duration of this study were not sufficient to compare recurrence rates. The issue of recurrence and its effect on cost-effectiveness is dealt with by the modelling in Chapter 6.

Group 3 trial

The Group 3 trial was the largest and most robust of the studies, and compared surgery with conservative treatment in those with more extensive varicose veins. The major deficiency of this trial is the limited duration of follow-up, as the majority of patients who were initially allocated to conservative treatment subsequently elected to undergo surgery. Despite this, the trial showed convincing and statistically significant differences at 1 year, with surgical treatment providing improved symptomatic relief, appearance, patient satisfaction and HRQoL. Once again, it must be remembered that this is a selected cohort of patients who were referred for treatment of their varicose veins, and may therefore have had expectations of active intervention, resulting in dissatisfaction amongst those who were randomised to conservative treatment.

Complications of treatment

A number of serious complications of surgery were encountered, in keeping with those that have been reported elsewhere.[197] These included DVT, nerve damage, chest infection and wound infections/cellulitis requiring readmission to hospital.

The overall rate of wound infections was 5.6%; however, this was based on patients' self-reported infections, and in the majority of these the problem resolved quickly following a single visit to a GP.

One limitation of the study was that venous imaging was not repeated after treatment. This might have identified asymptomatic DVT or persistent reflux following treatment. Such investigation would, however, have added significantly to the resource requirements and the inconvenience to participants and it was considered that the additional information did not justify this, particularly as the main outcomes of interest related to clinical and cost-effectiveness.

Quality of life measures

Several measures of outcome have potential to be used for the generation of the utilities for cost-effectiveness analysis. Both SF-6D and EQ-5D can generate societal utilities and are used in the cost-effectiveness assessment in Chapter 5. VASs give a quick and simple measure of overall HRQoL, and showed changes that were broadly similar to those seen with the SF-6D and EQ-5D.

In order to produce a cost–utility index, it is necessary to provide a utility weight for each possible outcome of treatment. The methods that conform best to expected utility theory[202] are the standard gamble[203] and TTO.[204] Although both of these have theoretical advantages, they require fairly complex interview techniques, which require that the condition in question is evaluated in respect to a risk of death or change in life expectancy. There are problems with using such techniques for conditions which have a relatively minor impact on HRQoL.[205] Although methods of using intermediate anchor points have been described,[206,207] these are not well validated. In this study, the standard gamble was used at the initial assessment and at the 1-year follow-up assessment, but was not found to be sufficiently sensitive to identify changes in the HRQoL in this group of patients.

Some difficulties were encountered in using standard gamble for the current study. The method

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used to collect standard gamble required interview techniques, and was completed only at the initial assessment and at the 1-year interview. It was also found to be time consuming and some patients found it difficult to understand. It was also found that patients evaluated their HRQoL as very close to one using this technique, so it did not provide sensitivity for distinguishing changes of state in this population of relatively healthy patients.

Cost-effectiveness analysis

This aspect of the study was intended to evaluate the cost-effectiveness of the various interventions for varicose veins alongside the RCTs. Unfortunately, the number of patients recruited and the losses to follow-up meant that in Groups 1 and 2 it was impossible to provide meaningful estimates of cost-effectiveness. The data collected in these trials, along with the observational data, are used to consider these issues through economic modelling in Chapter 6.

The economic analysis that was attached to the Group 3 RCT showed that over a 2-year period there was a discounted additional cost associated with surgical treatment of £387.45, with a measured benefit of 0.054 QALY, representing an overall ICER of £7175 per QALY in the base-case analysis. These results were robust through a range of sensitivity analyses.

The economic component of the study indicates that, for patients with extensive varicosities and evidence of saphenofemoral or saphenopopliteal reflux, surgical treatment offers a modest health benefit for a relatively minor extra NHS cost relative to conservative treatment. These conclusions hold regardless of the elicitation technique used to calculate QALYs, and for a number of alternative assumptions relating to unit costs for varicose vein treatment.

It is important to note that the time horizon used for the cost-effectiveness analyses was relatively short at 24 months owing to the lack of adequate follow-up data beyond that time. In practice, one would expect the benefits of surgical treatment to endure over a longer period. The consideration of benefits beyond 24 months would be likely to result in a reduction in the value of the ICER, so enhancing the cost-effectiveness of surgery. The economic model in Chapter 6 considers the impact of a longer time horizon on the results obtained from the clinical and economic evaluations in more detail.

It has been reported that £30,000 appears, in the context of the NICE appraisals, to be the threshold of what the NHS can afford to pay for additional QALYs, unless there are other arguments for adopting the technology.[208] If £30,000 is taken as the maximum acceptable cost-effectiveness ratio, then on the basis of the results reported here for patients diagnosed with severe varicose veins, surgical treatment appears highly cost-effective.

Willingness to pay

Unfortunately, the overall response rate to the WTP survey was not high. However, the results confirmed our *a priori* expectations in that respondents indicated, on average, higher WTP values for treatment as the severity of varicose veins increased. Surgery was preferred by the majority of respondents (56%) for the treatment of moderate varicose veins and by most respondents (98%) for the treatment of severe varicose veins. In the case of treatment for mild varicose veins, conservative treatment was preferred by the majority of respondents and the mean WTP for conservative treatment was higher than that expressed for sclerotherapy. Although concerns have been raised about how best to deal with zero valuations and the effect on overall analysis,[209] this did not occur frequently in our data and is unlikely to have significantly influenced the results.

In theory, the WTP values may be used as an alternative measure of the benefits of alternative interventions for the treatment of varicose veins. However, in practice, given the relatively small number of respondents to this survey, the results should be interpreted with caution. There is also a concern that respondents in the UK NHS are not used to paying for healthcare and therefore may have difficulties in expressing a WTP value. The hypothetical nature of the exercise may have led to a degree of response bias whereby individuals state a higher WTP value because they are aware that they will not actually have to pay for the treatment in question. However, the inclusion of a WTP study provided a mechanism by which individuals can express a preference for cosmetic outcomes. The cosmetic appearance of the leg may be an important factor to many patients. This may not be captured in the measurement of QALYs through generic measures of health status which focus upon factors relating to physical, social and emotional functioning rather than cosmetic appearance *per se*.

Modelling

The use of modelling in healthcare situations is becoming increasingly widespread, and is used for modelling the economics of particular treatments.[210,211] assisting in the planning of clinical trials and considering the potential benefit of additional information.[212] It may be particularly useful where high-quality primary research is difficult for practical or ethical reasons, or when decision-making may be required prior to the availability of high-quality data or long-term follow up from clinical trials.[213]

In the current study, there were difficulties in recruiting and randomising a large enough cohort of patients to provide robust clinical data. This was the case particularly in relation to sclerotherapy in patients with relatively minor varicose veins, owing to the limited number of referrals of patients in this group. Owing to the possible importance of late recurrence of varicose veins, it is also necessary to consider long-term outcomes that extend past the follow-up period of the current trial, and this has been addressed by modelling the situation using a 10-year time horizon.

By its nature, modelling requires a number of simplifications and assumptions, so it is important to be able to assess the validity of the model. This has been done, as far as possible, by comparing the outputs of the model with evidence from primary and published research regarding clinical outcomes. There are a number of difficulties with this approach; for example, the literature contains very little detailed information about recurrence rates for varicose veins structured in a suitable way to allow comparison with the model. The cohort analysis of the model does suggest, however, that the predicted rates of recurrence and retreatment are in keeping with observed experience. The model also generates similar results to the cost-effectiveness study reported in Chapter 5 when the time horizon is reduced to 2 years to correspond to that in the clinical study.

In practice, there was little difference between the populations treated within and outside the RCTs. This being the case, the data from the observational study were used to provide estimated values for an economic model of the management of varicose veins. This allowed the effect of doubt in parameters, such as costs and HRQoL weightings, to be addressed. It also made it possible to extrapolate from the current clinical trial to examine the potential effect of late recurrence on overall cost-effectiveness. The results of this modelling added further support to those of the RCT for Group 3, showing a lower ICER of £1936 per QALY for surgical treatment. This improvement in cost-effectiveness is likely to be partly the effect of extending the time horizon of the model to 10 years, compared with the 2-year time frame of the trial. Sensitivity analysis based on the 2-year time horizon showed that the model closely matched the results of the economic analysis.

Overall, the model provided consistent and robust findings across a range of sensitivity analyses, suggesting that surgical treatment for varicose veins provides benefits over conservative management and sclerotherapy, at a cost that would appear well within the thresholds of cost-effectiveness that are generally considered acceptable for the provision of services by the NHS.[214]

With regard to sclerotherapy, the results of the clinical trial were equivocal because there were insufficient data to carry out a meaningful economic analysis based directly on the trial. However, the results of the economic modelling suggested that sclerotherapy provides a modest benefit of about 0.044 QALY at a small incremental cost of £155. Although the overall benefit is small, it nevertheless suggests that it is a cost-effective treatment. However, in those patients for whom surgery is also an option, surgery is likely to provide greater benefit at a lower cost per QALY (exhibiting extended dominance). These results are robust across a wide range of different assumption and sensitivity analyses.

The development of this model has considerable potential to provide assistance in other areas where there is inadequate clinical information. These include the possibility of considering the potential benefit of new or novel treatments for varicose veins and the likely value of any further clinical trial. There is also the potential to consider other specific areas within the management of varicose veins, such as the potential cost-effectiveness of routine duplex scanning and the effect of policies regarding patient selection and waiting list management.

The economic modelling suggests that one of the major issues in determining the cost-effectiveness of the treatment of varicose veins is the valuation that is attached to any benefit obtained from the treatment. In this study, the base-case analysis used QALYs calculated from the SF-6D index, derived from the SF-36 questionnaire for HRQoL.[188] There is considerable debate regarding the most appropriate measures of outcome for

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cost-effectiveness analysis. In the case of varicose veins, the condition causes little disability, with most patients seeking treatment for cosmetic concerns or relatively minor symptoms affecting the legs.

Both the SF-6D and EQ-5D measures[215] use a series of generic questions to elicit HRQoL, which can then be converted to a utility score based on previous validated techniques using societal valuations. For setting priorities in healthcare, it is felt by some that a societal prospective is more appropriate for the calculation of utilities.[216] In this study, the SF-6D and the EQ-5D produced similar results. The former was chosen for the base-case analysis, owing to the potential concern that the EQ-5D might be less sensitive in picking up minor changes in HRQoL owing to the limited number of questions and potential responses.[215] The trial also used the VAS based on the 'EuroQol thermometer' and, although this gives similar results and is quick and simple to administer, it has a disadvantage that it does not provide a societal perspective and is not consistent with expected utility theory.[217]

Another issue in relation to the measurement of utility is that the QALY model takes little account of preferences for treatment that relate more to the process of care than to the outcome. In this study, the WTP exercise was carried out in order to look at patients' preferences in this respect. The results of the WTP exercise suggested that surgical treatment was more often preferred to sclerotherapy and that the strength of preference, as measured by the WTP, was greater for surgical treatment. This might seem to contradict expectations that a less invasive treatment would be preferred, and it may be that this outcome is distorted by preconceived ideas amongst the subjects that surgery has better or more lasting benefits, or may reflect a tendency to put a higher figure on surgical treatment owing to an expectation that surgery is more expensive than injection sclerotherapy.

In view of the number of new techniques that have the potential advantage of being less invasive then conventional surgery, such as foam sclerotherapy and laser or radiofrequency ablation of the LSV,[66,67,69,70,75] it may be important in the future to look at other techniques that allow process utilities to be incorporated in cost-effectiveness analysis.[218,219]

Conclusions

The RCT comparing surgery with conservative treatment for patients with more severe varicose veins provided good evidence of a significant benefit from surgical treatment in terms of symptomatic relief, anatomical extent of varicose veins, HRQoL and patient satisfaction.

The limited recruitment and small number of referrals of patients with minor varicose veins meant that no robust conclusions could be drawn from the RCTs about the relative merits of sclerotherapy. Another limitation of this study is that, by its nature, it relates to a selected population of patients referred to secondary care. If treatments for varicose veins were to be more widely and easily accessible, then it is possible that the extension of treatment to a wider population would reduce overall cost-effectiveness.

The literature reviews and primary research reported in this study show no evidence of benefit for surgery in terms of the prevention of long-term complications, particularly leg ulceration (in patients who have never had an ulcer), although this fear is known to be a reason why many patients seek treatment.[6] On the current evidence, the benefit of varicose vein treatment is limited to the alleviation of symptoms or cosmetic concerns related to varicose veins in those patients whose HRQoL is impaired by these complaints. However, the sensitivity analysis with the modelling suggests that if there were a reduction in long-term complications this would result in a further modest improvement in the overall cost-effectiveness of surgery.

Varicose veins represent a considerable management problem for the NHS because they are common and the demand for treatment is high. However, as varicose veins generally cause minor symptoms and rarely have a significant serious impact on health, they are afforded low priority and, in the absence of dedicated resources, this results in persistent waiting lists for treatment. This study suggests that the treatment is cost-effective and that the low priority given to varicose vein treatments ought therefore to be reconsidered. The economic modelling suggests that delays in treatment due to waiting lists are likely to reduce the cost-effectiveness of varicose vein treatment and are therefore counter-productive.

Implications for healthcare

The results of this study show that for patients seeking treatment for varicose veins, both surgery and sclerotherapy are cost-effective, within the limits generally considered appropriate for provision of services within the NHS.

In those patients for whom both treatments would be considered appropriate, surgery is expected to produce greater average benefit at a lower cost per QALY, making it the preferred option from both the patient and the NHS perspective.

Surgery has a small but significant rate of major complications (about 1%), but sclerotherapy has a high rate of recurrence and therefore provides smaller expected benefit. Patients and clinicians need to be aware of these factors when making treatment decisions.

New invasive techniques and physical and drug treatments do not have a good evidence base and, where these have additional costs, it is difficult to justify them other than as a part of further clinical studies.

Implications for research

This trial has demonstrated some of the difficulties in carrying out research into the management of varicose veins, particularly in terms of recruiting sufficient numbers of patients who are prepared to be randomised, and in following them up for an adequate period to take account of potential long-term differences in recurrence rates. In view of the findings of this study and the results of the economic modelling, it is questionable whether it would be practical, or whether there would be sufficient equipoise amongst clinicians, to carry out further direct comparisons of these treatments in RCTs. There are a number of areas in which the collection of more accurate data could inform further economic modelling, which might help to clarify the place of different or new treatment options. There are several areas where further research might be beneficial.

Development of large observational data sets

There is considerable uncertainty regarding the factors that influence the rate of recurrence of varicose veins. Many of the published trials with long-term follow-up were undertaken in the days before assessment with HHD or duplex scanning was available. It would be helpful to have more detailed information regarding the factors that are predictive of complications of treatment or recurrence of varicose veins. In any such study, it would also be helpful to collect information about the effects of conservative measures, such as compression hosiery and exercise in relation to symptoms. The benefits of such studies would be greater if consensus could be achieved regarding a standardised form of evaluation and grading of the severity of varicose veins.

Outcomes

One of the key issues in determining the cost-effectiveness of treatments for varicose veins is an understanding of their impact upon HRQoL. There is no general agreement as to the best method of measurement of utility in this condition. The identification of a suitable and generally accepted methodology would be a great advantage in this and other conditions for which the valuation of minor levels of impairment of utility are key issues in establishing cost-effectiveness. Such research would need to include the development and validation of appropriate methodology and to deal with the issues around the perspective from which utility should be measured.

With a condition such as varicose veins that has a relatively minor impact on overall health, it is important to consider other issues that may impact on the decision to provide services. These include issues surrounding the incorporation of process utility, individual patient preferences and healthcare priorities into the decision-making process. There is also evidence of unrealistic expectations and preconceptions amongst those referred for treatment and more research into educational methods and techniques to improve shared and informed decision making may be beneficial.

New treatments

There are a number of new treatments for varicose veins. Since some of these techniques (such as laser or radiofrequency occlusion of the LSV) are costly compared with conventional treatment, and the expected benefits are small, it would need a very large clinical trial to demonstrate their cost-effectiveness when compared with conventional surgery. In view of the considerations above, it may be difficult to achieve such a trial, and it might be helpful to examine such techniques, in the first instance, through the collection of observational data and their use to inform economic modelling.

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Contribution of authors

Jonathan Michaels (Professor of Vascular Surgery) had the original idea for the project, co-wrote the project protocol, supervised the project, analysed data, contributed to chapters in the final report and edited the final report. Bruce Campbell (Consultant Vascular and General Surgeon) co-wrote the project protocol, supervised the Exeter part of the project, analysed data and wrote chapters for the final report. John Brazier (Professor of Health Economics) co-wrote the project protocol, supervised the health economics aspects of the project and contributed to the economic analysis chapter. Jacqueline MacIntyre (Research Nurse) co-ordinated patient recruitment in Exeter, analysed data and contributed to chapters in the final report. Simon Palfreyman (Senior Research Nurse) co-ordinated patient recruitment in Sheffield, analysed data and contributed to the systematic reviews and chapters in the final report. Julie Ratcliffe (Senior Research Fellow) undertook the economic analysis and contributed to chapters in the final report. Kathryn Rigby (Specialist Registrar, General Surgery) undertook the systematic reviews and contributed to chapters in the final report.

The views and opinions expressed in the report are those of the authors alone.

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Appendix 1

Search strategy

Thirteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature (including current research). In addition, the reference lists of relevant articles were checked and various health services research related resources were consulted via the Internet. These included health economics and HTA organisations, guideline producing agencies, generic research and trials registers, and specialist sites.

Search restrictions

Where possible (e.g. in the smaller databases), searches were not restricted by publication type or study design. However, methodological filters aimed at identifying guidelines, systematic reviews, and clinical trials were applied in the larger databases, such as MEDLINE. Date and language restrictions were not used.

Electronic bibliographic databases searched

1. AMED
2. Best Evidence
3. Biological Abstracts
4. CCTR (Cochrane Controlled Trials Register)
5. CDSR (Cochrane Database of Systematic Reviews)
6. EMBASE
7. HMIC (Health Information Management Consortium - comprising DH-Data, the King's Fund Database, and Helmis)
8. Medline
9. NHS DARE (Database of Assessments of Reviews of Effectiveness)
10. NHS EED (Economic Evaluations Database)
11. NHS HTA (Health Technology Assessment)
12. PubMed (last 180 days)
13. Science Citation Index

Other sources searched

1. AHRQ (Agency for Healthcare Research and Quality)
2. ARIF (Aggressive Research Intelligence Facility)
3. Bandolier
4. CCOHTA (Canadian Co-ordinating Centre for Health Technology Assessment)
5. CCT (Current Controlled Trials)
6. CenterWatch Trials Register
7. ClinicalTrials.gov, NIH Clinical Trials Database
8. COIN (Department of Health Circulars)
9. CRiB (Current Research in Britain)
10. CRW (Current Research Worldwide)
11. Department of Health
12. eMC (Electronic Medicines Compendium)
13. Health Care Needs Assessment
14. Health Evidence Bulletins, Wales
15. HSTAT (Health Services/Technology Assessment Text, US National Library of Medicine)
16. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
17. Index to Theses
18. ISTP (Index to Scientific and Technical Proceedings)
19. MRC (Medical Research Council) Funded Projects Database
20. National Guideline Clearinghouse
21. National Research Register
22. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
23. NHS CRD (Centre for Reviews and Dissemination), University of York
24. NHS R&D Programmes
25. OMNI (Organising Medical Networked Information)
26. POINT (Department of Health publications)
27. ReFeR (Research Findings Register)
28. ScHARR Library Catalogue
29. SIGN (Scottish Intercollegiate Guidelines Network)
30. SumSearch
31. Trent Working Group on Acute Purchasing
32. TRIP (Turning Research into Practice) Database
33. UK Official Publications
34. Uncover

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35. Wessex DEC (Development and Evaluation Committee) Reports
36. West Midlands DES (Development and Evaluation Services) Reports

Search strategies used in the major databases

CDSR and CCTR 2000, Issue 4 (Updated 2001, Issue 3)

The Cochrane Library, Update Software (CD ROM version) Search undertaken April 2000 (Updated March 2001)

#1 varicose-veins*:ME
#2 saphenous-vein*:ME
#3 (varicose near5 vein*)
#4 (saphenous near5 vein*)
#5 #1 or #2 or #3 or #4
#6 surgery*:ME
#7 surgical-procedures-operative*:ME
#8 surg*
#9 ligation*:ME
#10 sclerotherapy*:ME
#11 strip*
#12 ligation*
#13 avulsion*
#14 #(high tie or high-tie)
#15 sclerotherapy
#16 (compression near5 stocking*)
#17 (compression near5 hosiery)
#18 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17#19 #5 and #18

Embase 1980–2001 SilverPlatter WebSPIRS

Search undertaken April 2000 (Updated March 2001)
#1 varicosis / all subheadings
#2 explode leg varicosis / all subheadings
#3 saphenous vein / al subheadings
#4 (varicose near5 vein*) in ti, ab
#5 (saphenous near5 vein*) in ti, ab
#6 #1 or #2 or #3 or #4 or #5
#7 surgery / all subheadings
#8 surgical technique / all subheadings
#9 surg* in ti, ab
#10 ligation / all subheadings
#11 explode vein ligation / all subheadings
#12 sclerotherapy / all subheadings
#13 strip* in ti, ab
#14 ligation* in ti, ab
#15 avulsion* in ti, ab
#16 (high-tie or high tie) in ti, ab
#17 sclerotherapy in ti, ab
#18 (compression near5 stocking*) in ti, ab
#19 (compression near5 hosiery) in ti, ab
#20 tourniquet* in ti, ab
#21 Esmarch in ti, ab
#22 Lofquist in ti, ab
#23 Cuff in ti, ab
#24 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or#19 or # 20 or #21 or #22 or #23
#25 #6 and #24

Medline 1966–2001 Ovid Biomed

Search undertaken April 2000 (Updated October 2000 and March 2001)
1 exp varicose veins/
2 saphenous vein/
3 (varicose adj5 vein$).tw
4 (saphenous adj5 vein$).tw
5 or/1-4
6 surgery/
7 exp surgical procedures, operative/
8 surg$.tw
9 ligation/
10 sclerotherapy/
11 strip$.tw
12 ligation$.tw
13 avulsion$.tw
14 (high tie or high-tie).tw
15 sclerotherapy.tw
16 tourniquet.tw
17 Esmarch.tw
18 Lofquist.tw
19 Cuff.tw
20 (compression adj5 stocking$).tw
21 (compression adj5 hosiery).tw
2 or/6-19
23 5 and 22

Methodological search filters used in Ovid Medline

Guidelines

1 guideline.pt
2 practice guideline.pt
3 exp guidelines/
4 health planning guidelines/
5 or/1-4

Systematic reviews

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw
4 meta analysis.pt
5 review academic.pt
6 review literature.pt
7 letter.pt

8 review of reported cases.pt
9 historical article.pt
10 review multicase.pt
11 or/1-6
12 or/7-10
13 11 not 12

Randomized controlled trials

1 randomized controlled trial.pt
2 controlled clinical trial.pt
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 or/1-5
7 clinical trial.pt
8 exp clinical trials/
9 ((clin$ adj25 trial$)).ti, ab
10 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti, ab
11 placebos/
12 placebos.ti, ab
13 random.ti, ab
14 research design/
15 or/7-14
16 comparative study/
17 exp evaluation studies/
18 follow up studies/
19 (control$ or prospectiv$ or volunteer$)).ti, ab
20 prospective studies/
21 or/16-20
22 6 or 15 or 2

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Appendix 2

Information sheets

PATIENT INFORMATION SHEET

A COMPARISON OF DIFFERENT TREATMENTS FOR VARICOSE VEINS

General Information

Varicose veins are very common and seldom cause serious medical problems. For people who want treatment there are three choices:

- Support stockings can control aching effectively.
- Injections (sclerotherapy) can be used to seal off the varicose veins.
- Operation (under general anaesthetic) removes the veins.

We need more information about the relative merits of these treatments because:

- The information about them was obtained in the years before we were able properly to scan veins using the modern ultrasound scanners which show exactly what is going on in the varicose veins and deeper veins.

- There is insufficient information about whether and how much each kind of treatment improves people's quality of life.

- Little is known about the cost effectiveness of these treatments. In many parts of the country restrictions have been placed on the treatment of varicose veins because they are not medically harmful. Decisions like this need to be informed by good information about cost effectiveness. Health Authorities, which are responsible for funding these treatments, may in the future, consider whether they will have funds to provide this full range of treatments.

The aim of this study is to compare different treatments for varicose veins in detail. All patients joining the various parts of this study will have their veins fully scanned, and will be asked in detail about the effect of varicose veins on their lives both before and after treatment. Depending on the kind of varicose veins you have, you will be asked if you would be prepared to join one or other part of this study. The different parts of the study compare different treatments. After you have been seen and assessed in the clinic you will be given further information about the particular treatment options that are appropriate in your case. If you agree to join the study then you will receive one or other of these treatments by a process of random allocation.

As with any medical study you are free to choose not to join the study. You may also leave the study at any time if you wish. In either case we would still very much like to see how you get on by sending you questionnaires and inviting you for an interview – just as if you had taken part in the randomised study.

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Groups 1 to 4 Information Sheets

PATIENT INFORMATION SHEET

A COMPARISON OF DIFFERENT TREATMENTS FOR VARICOSE VEINS

Group 1 Randomised study of conservative treatment or injection sclerotherapy

You have varicose veins that look suitable for treatment by injections (sclerotherapy) rather than operation. This treatment is given in the outpatient clinic and involves injection of a chemical into the varicose veins, which causes them to seal off. Injections are placed in the obvious varicose veins using a fine needle. The injected areas are covered with pads and the leg is covered with a firm stocking or bandage for two or three weeks. Sometimes two or three visits to clinic are required to get rid of all the noticeable veins. Sometimes there is a little inflammation after the injections, and occasionally there can be some permanent brown staining but, in general, we would expect to get your veins sealed off by this treatment. Time off work should not be necessary after injection treatment. We would give you a more detailed advice sheet about all this. The uncertainty about injection treatment is how well it works in the long term. Many people find that their veins come back – even within a year or two. Many hospitals do not use injection treatment at all because they do not feel that it is worthwhile. This is why a major part of the present study is designed to compare the use of injections against conservative treatment.

Conservative treatment consists of advice to you about lifestyle, exercise and leg elevation, and the use of compression hosiery (stockings).

- Whether or not you are randomised to injection sclerotherapy or conservative treatment we would examine you and ask you questions in just the same way. At your initial visit we would ask you to complete a questionnaire, interview you, examine your leg/s and later perform a duplex ultrasound scan of the veins. This scan is painless and shows exactly what is going on in the varicose veins and the deeper veins.

- One month after your treatment or initial visit we would ask you to complete a detailed questionnaire about your symptoms and quality of life.

- At six months, one year, and two years we would ask you to complete a similar questionnaire. At one year we would like to have a brief interview with you and examine your leg/legs again.

- We are hoping to follow as many patients as possible beyond the two-year stage and will discuss with you the possibility of finding out how you are up to five years after your initial visit.

If, at two years, you are dissatisfied with the result of treatment (or no treatment), then we would be pleased to discuss the possibility of further treatment with you.

If you want more information or if you are worried at any time, please contact Simon Palfreyman, Research Nurse on 0114 226 6798.

PATIENT INFORMATION SHEET

A COMPARISON OF DIFFERENT TREATMENTS FOR VARICOSE VEINS

Group 2 Randomised study of injection sclerotherapy or surgical treatment

You have varicose veins which look suitable for treatment by injections (sclerotherapy) or by operation.

Injection treatment is given in the outpatient clinic and involves injection of a chemical into the varicose veins which causes them to seal off. Injections are placed in the obvious varicose veins using a fine needle. The injected areas are covered with pads and the leg is covered with a firm stocking or bandage for two or three weeks. Sometimes two or three visits to clinic are required to get rid of all the noticeable veins. Sometimes there is a little inflammation after the injections, and occasionally there can be some permanent brown staining but, in general, we would expect to get your veins sealed off by this treatment. Time off work should not be necessary after injection treatment. We would give you a more detailed advice sheet about all this. The uncertainty about injection treatment is how well it works in the long term. Many people find that their veins come back – even within a year or two. Many hospitals do not use injection treatment at all because they do not feel that it is worthwhile. This is why a major part of the present study is designed to compare the use of injections against surgical treatment.

Surgical treatment for varicose veins involves a general anaesthetic and a number of incisions on your leg/s. This is sometimes done as a day case and sometimes as an inpatient. At your initial visit we will give you a very detailed booklet about this kind of surgery which includes information on the pros and cons; exactly what happens when you come into hospital; advice about your recovery; and information about possible problems. Some tenderness and discomfort are normal after operation and time off work is usually necessary. Bruising is common, and some people are very bruised; this settles over a period of weeks. Support stockings are advised for about ten days after operation. Surgery generally gives a good long-term result, although some patients do develop further varicose veins over the years.

- Whether or not you are randomised to injection sclerotherapy or surgical treatment we would examine you and ask you questions in just the same way. At your initial visit we would ask you to complete a questionnaire, interview you, examine your leg/s and later perform a duplex ultrasound scan of the veins. This scan is painless and shows exactly what is going on in the varicose veins and the deeper veins.

- One month after your treatment or initial visit we would ask you to complete a detailed questionnaire about your symptoms and quality of life.

- At six months, one year, and two years we would ask you to complete a similar questionnaire. At one year we would like to have a brief interview with you and examine your leg/legs again.

- We are hoping to follow as many patients as possible beyond the two-year stage and will discuss with you the possibility of finding out how you are up to five years after your initial visit.

If, at two years you were dissatisfied with the result of treatment (or no treatment), then we would be pleased to discuss the possibility of further treatment with you.

If you want more information or if you are worried at any time, please contact Simon Palfreyman, Research Nurse on 0114 226 6798.

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PATIENT INFORMATION SHEET

A COMPARISON OF DIFFERENT TREATMENTS FOR VARICOSE VEINS

Group 3 Randomised study of conservative treatment or surgical treatment

Surgical treatment for varicose veins involves a general anaesthetic and a number of incisions on your leg/s. This is sometimes done as a day case and sometimes as an inpatient. At your initial visit we will give you a very detailed booklet about this kind of surgery which includes information on the pros and cons; exactly what happens when you come into hospital; advice about your recovery; and information about possible problems. Surgery generally gives a good long-term result, although some patients do develop further varicose veins over the years.

In many parts of the country health authorities and surgeons restrict the use of surgery for varicose veins for people who have not got serious symptoms. This study aims to show whether surgery improves people's quality of life and also to document its cost effectiveness.

Conservative treatment consists of advice to you about lifestyle, exercise and leg elevation, and the use of compression hosiery (stockings).

- Whether or not you are randomised to conservative treatment or surgical treatment we would examine you and ask you questions in just the same way. At your initial visit we would ask you to complete a questionnaire, interview you, examine your leg/s and later perform a duplex ultrasound scan of the veins. This scan is painless and shows exactly what is going on in the varicose veins and the deeper veins.

- One month after your treatment or initial visit we would ask you to complete a detailed questionnaire about your symptoms and quality of life.

- At six months, one year, and two years we would ask you to complete a similar questionnaire. At one year we would like to have a brief interview with you and examine your leg/s again.

- We are hoping to follow as many patients as possible beyond the two-year stage and will discuss with you the possibility of finding out how you are up to five years after your initial visit.

If, at two years you were dissatisfied with the result of treatment (or no treatment), then we would be pleased to discuss the possibility of further treatment with you.

If you want more information or if you are worried at any time, please contact Simon Palfreyman, Research Nurse on 0114 226 6798.

PATIENT INFORMATION SHEET

A COMPARISON OF DIFFERENT TREATMENTS FOR VARICOSE VEINS

Group 4 Observational Study

This is part of a study comparing different treatments for varicose veins but is the part of the study in which people are not randomised to receive any particular treatment. A decision about your treatment is being made in the normal way by discussion between yourself and hospital specialists.

We are, nevertheless, keen to find out in detail about your varicose veins and about the effect of treatment on your leg and your quality of life (just as if you had joined in a randomised part of the study). This will mean

- At your initial visit we would ask you to complete a questionnaire, interview you, examine your leg/s and later perform a duplex ultrasound scan of the veins. This scan is painless and shows exactly what is going on in the varicose veins and the deeper veins.
- One month after your treatment or initial visit we would ask you to complete a detailed questionnaire about your symptoms and quality of life.
- At six months, one year, and two years we would ask you to complete a similar questionnaire. At one year we would like to have a brief interview with you and examine your leg/s again.
- We are hoping to follow as many patients as possible beyond the two-year stage and will discuss with you the possibility of finding out how you are up to five years after your initial visit.

If you want more information or if you are worried at any time, please contact Simon Palfreyman, Research Nurse on 0114 226 6798.

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CONSERVATIVE TREATMENT INFORMATION SHEET

PATIENT INFORMATION SHEET

Information regarding:

CONSERVATIVE MEASURES FOR VARICOSE VEINS

Weight: Being overweight increases symptoms from varicose veins and may make the veins get worse more quickly. We will tell you your ideal body weight, and if you are heavier than this, then you would be well advised to lose weight, aiming at your ideal figure.

Exercise: Regular exercise of any kind is a good idea. Walking is sufficient, but any leg exercise is beneficial (jogging, cycling, swimming, etc.). Long periods of activity (e.g. 'walk three miles') are not necessary: shorter yet frequent activity is quite adequate.

Work: Jobs that involve prolonged standing make varicose veins worse. If you have to stand for long periods, then wearing support, moving your legs, or going for short walks during the working day may help your symptoms.

Elevation: Putting your feet up helps to relieve symptoms, especially at the end of the day. You should aim to get your feet at least the same level as your hips: up on a sofa or bed, or resting on another chair (not on a footstool – most footstools or poofs are too low).

Support stockings or tights: Support hosiery helps to counteract the high pressure in the veins and relieves symptoms, but it must be well fitted and comfortable. Various kinds of support stockings and tights are available at chemists and other shops. For men, below knee compression stockings are made in a variety of colours, which look like ordinary long socks. Stronger stockings (graduated compression stockings) are available either on prescription, or on sale at chemists and surgical appliance stores. Below knee graduated compression stockings are usually adequate, but full length ones are available. They are graded as Class I (often enough to control aching from varicose veins), Class II (medium strength, and most often prescribed by specialists), and Class III (very supportive, and generally for people with serious symptoms).

Pregnancy: Varicose veins often appear in pregnancy and further pregnancies tend to make them worse. If varicose veins are treated by surgery or injections, subsequent pregnancy may cause them to come back.

Remember: Varicose veins are usually harmless and seldom cause serious medical problems. Following the advice above may be quite enough to control your symptoms.

SCLEROTHERAPY INFORMATION SHEET

PATIENT INFORMATION SHEET

Advice to patients having:

SCLEROTHERAPY

This is usually suitable only for relatively small varicose veins that are unsightly but cause no symptoms. It works by injecting a chemical (a sclerosant) into the varicose vein that causes the vein to seal off. The injected areas are covered with pads and the leg is covered with a firm stocking or bandage for two or three weeks. Sometimes two or three visits to clinic are required to get rid of all the noticeable veins. Sometimes there is a little inflammation after the injections, and occasionally there can be some permanent brown staining but, in general, we would expect to get your veins sealed off by this treatment.

Before your next visit

Please make sure you have stopped taking the oral contraceptive pill, which theoretically could increase the risk of serious thrombosis. This could be stopped one month before your appointment but it is very important to think about an alternative contraceptive method until after your treatment.

There is little evidence that low dose 'mini-pills' and hormone replacement therapy (HRT) need to be stopped

At the Clinic

A small amount of sclerosant is injected into the vein at one or more sites and a rubber pad applied. An elastic bandage or stocking will then be applied.

Usually one leg is treated at one visit and so repeat injections will be required if both legs are affected **or** you have many veins in one leg.

Please do not drive yourself home from the clinic. Arrange for somebody to collect you. Or you can take a bus or taxi. Please take a short walk as soon as possible after the injection as this will help to clear any remaining sclerosant from the leg.

The injection site may sting afterwards. Paracetamol should help relieve any discomfort.

Afterwards

For the first 24 hours rest as much as possible, sitting with your feet elevated above the level of the hips. Take a few short walks and try to avoid standing still for any length of time.

After 48 hours you can remove any bandages and pads applied. The stocking should be worn at all times during the day but can be removed in bed and when taking a bath or shower. Once the bandages and pads are removed you may drive.

The success of the injection treatment relies upon the pressure the bandage and stocking apply to the injected area. You can stop wearing the stocking when the leg is completely comfortable on standing – usually 3 to 4 weeks.

What to expect after the injections

Over the first few weeks after the injection, any slight discomfort, hardness or tenderness at the site(s) should subside.

If there is excessive redness, swelling or tenderness you should rest more with the leg raised so that the heel is higher than the hip.

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While most patients experience no problems after injection of varicose veins, a small number may experience one or more of the following:

- *A persistent hard 'cord' in the line of the vein.*
- *Brown staining of the skin in the line of the vein.*
- *Thread veins may develop if you are prone to them.*
- *Rarely, ulceration of the skin at the injection site(s).*
- *Failure of the injection to obliterate the vein.*

NOTE: It may be advisable for you to wear light support stockings or tights to prevent the occurrence of further varicose veins.

SURGERY INFORMATION SHEET

PATIENT INFORMATION SHEET

Information regarding:

VARICOSE VEIN OPERATIONS

INTRODUCTION

We expect you to make a rapid recovery after your operation and to experience no serious problems. However, it is important that you should know about minor problems that are common after surgery, and also about more serious problems that can occasionally occur. We would ask you to pay particular attention to the section headed "**What problems can occur after the operation?**" located near the end of this booklet.

HOW CAN VARICOSE VEINS BE TREATED BY AN OPERATION?

A cut is made over the top of the main varicose vein and it is tied off just where it joins the deep vein in the groin. This is closed with stitches, which are hidden under the skin.

The main vein under the skin is also stripped out. This helps to guard against varicose veins forming again. Blood flows up the many other veins in the leg after this vein has been removed.

Varicose veins marked before the operation are removed through tiny cuts. These cuts can be closed with stitches or adhesive strips.

Other veins under the skin with connections to the deep veins may also need to be dealt with – in particular one just above and behind the knee.

HOW LONG WILL I HAVE TO WAIT FOR MY VARICOSE VEIN OPERATION?

We do not like to keep people waiting for long periods of time but have to deal with patients according to their medical priorities. Those with more serious symptoms, such as skin changes or ulcers as a result of varicose veins, take priority over those with aching or cosmetic embarrassment.

Delays are caused by heavy demands on staff and resources, and there are particular problems in dealing with varicose veins because large numbers of patients are referred to hospital and operating on them takes quite a long time. This means that there is a limit on the number of varicose vein operations which can be done, while dealing at the same time with other conditions that are a serious threat to life or health. Some health authorities have experienced such difficulty in offering treatment to all patients referred with varicose veins that they will not treat people with "cosmetic" varicose veins at all.

WHAT ABOUT THE ANAESTHETIC?

The anaesthetic is one of the main concerns for all patients. This worry is understandable but modern anaesthetics are very safe and serious complications are uncommon.

The operation is usually conducted under a general anaesthetic and lasts for about one hour for each leg.

HOW LONG WILL I SPEND IN HOSPITAL?

This depends on whether you are able to have surgery as a day case.

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Day-patient
If you are medically fit and have somebody at home with you then day case operation may well be possible. As a day-patient you are able to return home on the day of your operation.

Inpatient
If it is thought best that you come into hospital as an inpatient, you will usually be admitted the day before the operation for the doctors and nurses to assess your needs.

WHAT HAPPENS BEFORE THE OPERATION?

After coming into hospital you will meet the nurses (one of whom will be specially allocated to look after you), junior doctors, and the anaesthetist. They will conduct some basic tests and will answer any questions.

The consultant or member of the team will check all the necessary preparations have been made and will mark your varicose veins with a felt tip pen. Be sure that all the veins you would like dealt with have been marked, and ask about any that have not.

The consent form. The hospital will require you to sign a consent form.

Food. You should not have anything to **eat for 5 hours before** the operation, but you can have **clear fluids**, tea or coffee **up to 3 hours before** the operation. This is because an empty stomach is important for a general anaesthetic.

Shaving. The nurses will tell you on the day of the operation where you will need to shave. If you are going to have a cut in the groin this area will need to be shaved, but there will be no need to shave all the pubic hair.

WHAT HAPPENS AFTER THE OPERATION?

Pain Relief. People vary a lot in the amount of pain they experience after the operation, though most experience discomfort only. The groin area can cause some discomfort but we inject long acting local anaesthetic into the groin wound during the operation, which greatly reduces any pain you might feel. It is more uncomfortable to get up and walk after operation to both legs than when one leg has been dealt with. In either case you will be allowed to get up and walk on the day of the operation when the effects of the anaesthetic have worn off sufficiently.

Painkillers will be prescribed for you to take after the operation. If you experience any pain you should ask the nurse for these while in hospital. You should take them yourself at home if you are uncomfortable. It is important that you should take painkillers if you need them to walk about and to rest with comfort. You should not need them for more than a few days – but the duration of discomfort varies from person to person.

HOW WILL I MANAGE IN THE DAYS FOLLOWING MY OPERATION?

Day-patient
After two to three hours you should feel fit enough to go home. Before you leave the nurses will check your leg. They will give you a note for your GP and some painkillers to take home with you. You should also be given an advice sheet. Please feel free to ask questions about anything you did not understand. Arrangements will be made for a nurse to call at your home the next day, to check on you and change your bandages for a special support stocking.

Inpatient
You will usually be able to get up within a few hours of the operation. The bandages on your leg will be changed the day after your operation for a special support stocking. You will be able to go home as soon as you and the doctors agree that you are sufficiently well and mobile – usually on the first or second day after the operation.

WHAT ABOUT MY WOUNDS

Sometimes a little blood will ooze from the wounds during the first 12 to 24 hours after the operation. The amount is likely to be very small and bleeding usually stops on its own. If necessary, press on the wound for ten minutes with a dressing or pad of paper tissues.

If bleeding continues after doing this twice, phone the Day Case Centre, the ward or your GP. If you cannot contact any of these then come to the Accident and Emergency Department.

It is common for the area under the groin to feel tender for a few days and "thickened" for a few weeks. Areas of tender lumpiness may also be felt elsewhere on the legs. This is caused by some blood clotting under the skin in the places where the varicose veins were removed. It is not harmful and will gradually go away, but may take several weeks.

WILL I HAVE DRESSINGS OR STITCHES?

Often we do not use a dressing in the groin, but if there is one it can generally be taken off 2–3 days after the operation. After this time the groin wound can be washed normally with soap and water. Avoid talcum powder for the first few days.

Stitches in the groin do not have to be removed: they will simply dissolve. If there are any stitches that do need to be removed we will advise you clearly when they should be removed.

The cuts further down the leg are closed with adhesive strips. You should not bath or shower for 10 days unless you can do so without getting the adhesive strips wet. After this time you can remove the strips yourself: it is often easiest to bath or shower which helps loosen them.

It is not always possible to wash off all traces of antiseptic or blood from your legs at the end of the operation due to the adhesive strips. However, it will all be removed when you have a bath or shower ten days after the operation.

WHAT ABOUT BANDAGES AND SUPPORT STOCKINGS?

Your bandages will be changed for special support stockings a week after the operation. These stockings may be worn all the time. However, if find them uncomfortable at night you can take them off but remember to put them on again in the morning. They are mainly intended to support the leg while you are up and about during the day.

You can stop wearing these stockings 10 days after the operation – but if you feel more comfortable with them for another few days this is quite alright.

WILL MY LEGS BE BRUISED?

Bruising is common after varicose vein operations. This is sometimes quite extensive and may take a month or more to settle. In particular it can occur on the inner thigh, where there may be no cuts, due to stripping of the main vein under the skin from this area.

HOW FAR SHOULD I WALK?

You can start to walk about as soon after the operation as you are able. Getting up the next day is sometimes a little uncomfortable, particularly when the groin has been operated on. The whole leg may feel stiff and tender to touch in places. You will not damage any of the wounds by walking. Take painkillers if you need them.

You should aim to walk about every half-hour or so during the day for the first week or two. This often means simply getting back to your normal routine as rapidly as possible. Frequent walking is more important than walking a long distance.

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When you are not walking try and put your foot up. Avoid standing or sitting with the foot on the floor as much as you can for the first two weeks after the operation.

WHEN WILL I BE FULLY BACK TO NORMAL?

This varies a lot between different people, and depends on how large and extensive your varicose veins were. In particular your recovery will depend on whether you have had an operation on one or both legs.

If you have had surgery on one leg only:
You are likely to feel tired for the first 2 or 3 days and your leg will be stiff after walking long distance for about a week. By two weeks after the operation you're likely to be walking good distances with little discomfort, even though there may still be some bruising and tenderness.

If you have had surgery on both legs:
You are likely to feel tired for the first week, especially after walking a lot. It may be two or three weeks after the operation before you are walking really comfortably. Your legs may be a little tender and bruised for a month or more.

WHEN CAN I DRIVE A CAR?

You can drive as soon as you feel confident that you can make an **emergency stop without pain.** This is often about a week after surgery. If you are concerned check with your insurance company.

WHEN CAN I RETURN TO WORK AND PLAY SPORTS?

You can return to work and sporting activity as soon as you feel sufficiently well and comfortable. If your job involved prolonged standing or driving, then you should not consider going back for at least two weeks. It is unusual to need more than about three weeks off work after surgery to one leg, or four weeks after surgery to both legs.

Avoid violent sports while you are still in support stockings or bandages, and thereafter start with some gradual training, rather than in immediate competition. Do not go swimming until you are out of support stockings and all the wounds are dry.

WHAT PROBLEMS CAN OCCUR AFTER THE OPERATION?

Serious complications are uncommon after operations for varicose veins. Some bruising is usual and occasionally the leg becomes very bruised – it should all go away over a period of weeks.

Aches, twinges and areas of tenderness may all be felt in the legs for the first few weeks after the operation. These will all settle down, and should not discourage you from becoming fully active as soon as you are able.

Tender lumps under the skin are common and are caused by blood clots in the places where the veins were removed. They are not dangerous and will gradually be dissolved by the body over several weeks. Occasionally they can be quite painful during the first two weeks or more.

Infection is an occasional problem, particularly in groin wounds. If you are concerned this is problem visit your GP or call the Day Case Centre. It usually settles with antibiotic treatment.

The scars on your legs are noticeable to start with but will continue to fade for many months after the operation. Very occasionally, some people develop a little brown staining where the veins were removed or areas of tiny veins appearing in the skin nearby.

Numbness in some areas of the leg can be caused by nerves being damaged when removing veins close to them. The area of numbness will settle and get smaller over weeks or months. If varicose veins on the

foot are removed, damage to small nerves is a special danger. If a nerve lying alongside one of the main veins under the skin is damaged, then a larger area of numbness can be caused.

Damage to major arteries, veins and the main nerve which allows the leg to move normally have all happened during varicose vein operations, but are **very rare** complications, which we take great pains to avoid.

Deep vein thrombosis causes swelling of the leg and this can result in a blood clot passing to the lungs. It is a possible complication after varicose vein surgery. Sometimes, injections are given to make the blood clot less than normal: these reduce the risk of thrombosis but increase the bruising.

If you are taking the contraceptive pill your risk of thrombosis is increased. The surgeon will discuss with you the pros and cons of stopping the pill or continuing it and taking special measures to reduce your risk of a thrombosis. **If you start taking the contraceptive pill while waiting for your operation let the hospital know.**

General anaesthetics all involve some risks but considerable precautions are taken to keep these as low as possible.

WILL MY VARICOSE VEINS COME BACK?

Some people develop new varicose veins during the years after a varicose vein operation, but this is uncommon after thorough surgery. Rarely, varicose veins simply re-grow in the areas that have been dealt with. If veins develop again they can be dealt with by injections or a further operation should they become troublesome.

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Appendix 3A

Baseline assessment questionnaire

VARICOSE VEIN RESEARCH PROJECT

Patient Questionnaire

No. 1

PART ONE

The following questions ask for your views about your health and how well you are able to do your usual activities.

If you are unsure about how to answer any question, please give the best answer you can and make any comments in the space available after the questionnaire

1 In general would you say your health is:

Please tick one

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

2 Compared to one year ago, how would you rate your health in general now?

Please tick one

- Much better now than one year ago ☐
- Somewhat better now than one year ago ☐
- About the same ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

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HEALTH AND DAILY ACTIVITIES

3 The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

Please tick one box on each line

		Yes, limited a lot	Yes, limited a little	No, not limited at all	For office use
a.	*Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐	☐
b.	*Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐	☐
c.	Lifting or carrying groceries	☐	☐	☐	☐
d.	Climbing *several* flights of stairs	☐	☐	☐	☐
e.	Climbing *one* flight of stairs	☐	☐	☐	☐
f.	Bending, kneeling or stooping	☐	☐	☐	☐
g.	Walking *more than a mile*	☐	☐	☐	☐
h.	Walking *half a mile*	☐	☐	☐	☐
i.	Walking *100 yards*	☐	☐	☐	☐
j.	Bathing and dressing yourself	☐	☐	☐	☐

4 During the *past 4 weeks*, have you had any of the following problems with your work or other daily activities *as a result of your physical health*?

Answer Yes or No to each question

		YES	NO	For office use
a.	Cut down on the *amount of time* you spent on work or other activities	☐	☐	☐
b.	*Accomplished less* than you would like	☐	☐	☐
c.	Were limited in the *kind* of work or other activities	☐	☐	☐
d.	Had *difficulty* performing the work or other activities (e.g. it took extra effort)	☐	☐	☐

5 During the *past four weeks*, have you had any of the following problems with your work or other daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

Answer Yes or No to each question

		YES	NO	For office use
a.	Cut down on the *amount of time* you spent on work or other activities	☐	☐	☐
b.	*Accomplished less* than you would like	☐	☐	☐
c.	Didn't do work or other activities as *carefully* as usual	☐	☐	☐

6 During the *past four weeks*, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Please tick one

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7 How much *bodily* pain have you had during the past 4 weeks?

Please tick one

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very severe ☐

8 During the *past 4 weeks*, how much did pain interfere with your normal work (including work both outside the home and housework)?

Please tick one

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

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YOUR FEELINGS

9 These questions are about how you feel and how things have been with you during the past month. For each question, please indicate the one answer that comes closest to the way you have been feeling.

Please tick one box on each line

How much time during *the past month*

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time	For office use
a.	Did you feel full of life?	☐	☐	☐	☐	☐	☐	☐
b.	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐	☐
c.	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐	☐
d.	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐	☐
e.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐	☐
f.	Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐	☐
g.	Did you feel worn out?	☐	☐	☐	☐	☐	☐	☐
h.	Have you been a happy person?	☐	☐	☐	☐	☐	☐	☐
i.	Did you ever feel tired?	☐	☐	☐	☐	☐	☐	☐

10 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your *social activities* (like visiting friends or close relatives)?

Please tick one

All of the time ☐

Most of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

HEALTH IN GENERAL

11 Please choose the answer that best describes how true or false each of the following statements is for you.

Please tick one box on each line

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false	
b.	I seem to get ill more easily than other people	☐	☐	☐	☐	☐	☐
b.	I am as healthy as anybody I know	☐	☐	☐	☐	☐	☐
c.	I expect my health to get worse	☐	☐	☐	☐	☐	☐
d.	My health is excellent	☐	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS ASK ABOUT OTHER WAYS IN WHICH THE TROUBLE WITH YOUR VARICOSE VEINS HAS AFFECTED YOU

12 Has your performance of daily activities or your job been limited?

Please tick one

A lot ☐
Moderately ☐
A little ☐
Not at all ☐

13 How long have your varicose veins been causing you problems? _____

14 Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

Please tick one

a) Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

b) Self-care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

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c) Usual Activities

I have no problems with performing my usual activities ☐
(*e.g. work, study, housework, family or leisure activities*)

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

d) Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

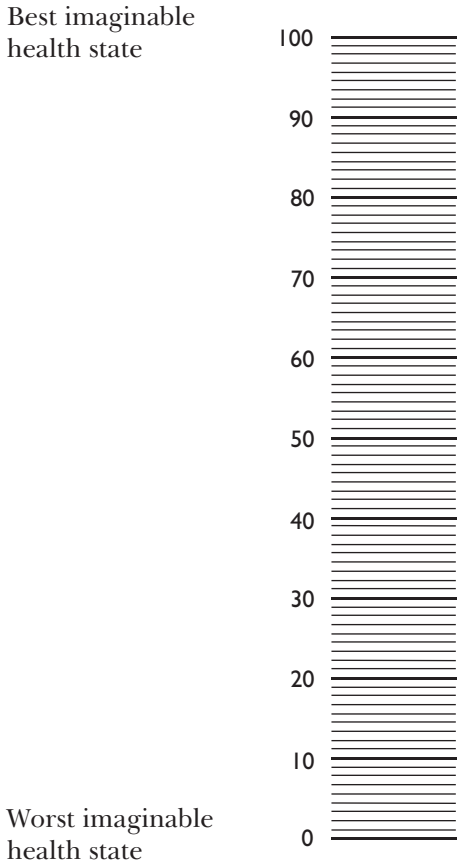
e) Anxiety/Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Please mark the scale on this page to show how you feel your overall health is today



FINALLY, SOME QUESTIONS ABOUT YOURSELF

15 What sex are you?

Male ☐
Female ☐

16 What is your date of birth?

Day	Month	Year
☐☐	☐☐	☐☐

17 Do you live with any other adults?

Yes ☐
No ☐

18 What is your current marital status?

Widowed ☐
Divorced/Separated ☐
Married or living as married ☐
Single and never been married ☐

19 What is your current employment status?

Working full-time (30 hours or more per week) ☐
Working part-time (less than 30 hours per week) ☐
Caring for home or family (not seeking paid work) ☐
Unemployed and looking for work ☐
Unable to work due to illness or disability ☐
Retired ☐

20 Are you in full-time education as a pupil/student?

Yes ☐
No ☐

If "No", how old were you when you left full-time education? _____ years

21 Do you, or have you, suffered from any of the following?

Diabetes ☐
Angina ☐
Stroke ☐
High blood pressure ☐
Breathing problems ☐

Other serious disease (please specify) .....

.....

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22 Are you currently a smoker?

Yes ☐

No ☐

23 If so, how many cigarettes per day? _____ cigarettes

24 Have you ever worn support stockings (or tights) for your varicose vein symptoms?

Yes ☐

No ☐

25 Do you regularly wear support stockings (or tights) now for your varicose vein symptoms?

Yes ☐

No ☐

25* Have you found support stockings (or tights) helpful in relieving your varicose vein symptoms?

Very helpful ☐

Quite helpful ☐

No effect at all ☐

They made my legs a little more uncomfortable ☐

They made my legs a lot more uncomfortable ☐

Have you any comments about your experience with support stockings (or tights)?

26 Where did you get your support stockings (or tights)?

Bought at the chemist ☐

Bought at other shop ☐

Prescribed by doctor and fitted at a chemist ☐

Other ☐

If "Other", please give details. _____

27 What length of support stockings (or tights) did you try (or are wearing now)?

Stockings thigh length ☐

Stockings knee length ☐

Tights ☐

[*Error in original form.]

28 What weight of support stockings (or tights) did you try (or are wearing now)?

Light weight ☐

Heavy weight ☐

29 What class of support stockings (or tights) did you try (or are wearing now)?

Class I ☐

Class II ☐

Class III ☐

30 What was the make or brand name of your support stockings (or tights)?

_____

31 Did you find it difficult to complete this questionnaire?

Yes ☐

No ☐

32 Approximately how long did it take you? _____ minutes

33 Did you have any assistance in completing this questionnaire?

Yes ☐

No ☐

34 Any other comments you would like to make?

_____

_____

_____

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Appendix 3B

Baseline assessment proforma

SHEFFIELD VASCULAR INSTITUTE
VARICOSE VEIN ASSESSMENT

Affix Sticker
Name:
D.O.B:
Number:

Hospital:

Date:

Assessor:

SYMPTOMS	**RIGHT**	**LEFT**
Aching	○	○
Itching	○	○
Heaviness	○	○
Swelling	○	○
Cosmetic Embarrassment	○	○
COMPLICATIONS		
Phlebitis	○	○
Eczema	○	○
Ulcer	○	○
Bleeding	○	○
PREVIOUS TREATMENT		
Surgery	○	○
Sclerotherapy	○	○

RISK FACTORS

DVT:

Leg Fracture:

Family History: Varicose Veins ☐ Ulcers ☐

PAST MEDICAL HISTORY

Smoker	Yes ☐	No ☐	Ex ☐	No./Day
Cardiac Problems	Yes ☐	No ☐	(Specify)	
Respiratory Problems	Yes ☐	No ☐		
Allergies	Yes ☐	No ☐	(Specify)	
Have worn Support Hosiery	Yes ☐	No ☐		

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MEDICATION (Including Hormonal Therapy)

Contraceptive pill Yes ◯ No ◯ HRT Yes ◯ No ◯

Height (cm) ☐☐☐ Weight ☐☐☐

BMI ☐☐

EXAMINATION

Assessor (initials) ☐☐☐

Clinical:	**Right**			**Left**		
Varicose veins in upper 1/3 thigh?	Yes ◯	No ◯		Yes ◯	No ◯	
	<5 mm ◯	◯ >5 mm	◯ none	<5 mm ◯	◯ >5 mm	◯ none
Varicose veins in upper 1/3 thigh?	Yes ◯	No ◯		Yes ◯	No ◯	
	<5 mm ◯	◯ >5 mm	◯ none	<5 mm ◯	◯ >5 mm	◯ none
Below knee varicose veins?	Yes ◯	No ◯		Yes ◯	No ◯	
	<5 mm ◯	◯ >5 mm	◯ none	<5 mm ◯	◯ >5 mm	◯ none

Extent (number of quadrants) ☐☐☐ ☐☐☐

DOPPLER Significant reflux >1 second	**Right**		**Left**	
Groin	Yes ◯	No ◯	Yes ◯	No ◯
LSV above knee	Yes ◯	No ◯	Yes ◯	No ◯
Popliteal fossa	Yes ◯	No ◯	Yes ◯	No ◯
Arterial Disease	Yes ◯	No ◯	Yes ◯	No ◯

DUPLEX SCAN INDICATED	**Right**		**Left**	
	Yes ◯	No ◯	Yes ◯	No ◯
Reason				
Popliteal fossa reflux	Yes ◯	No ◯	Yes ◯	No ◯
Recurrent varicose veins	Yes ◯	No ◯	Yes ◯	No ◯
Atypical varicose veins	Yes ◯	No ◯	Yes ◯	No ◯
History (previous fracture, DVT)	Yes ◯	No ◯	Yes ◯	No ◯

Discharged ☐

Randomisation Group ☐

Consent to Randomisation ☐

Result of Randomisation: Surgery ☐

Sclerotherapy ☐

Conservative ☐

If not randomised indicate reason:

	Mandatory exclusion (e.g. ulcers)
	Refused to participate
	Mandatory observation (e.g. recurrence)
	Refused randomisation, agreed to observation

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Appendix 3C

Standard gamble questionnaire

CHOICE "A"

You have no problems **walking** about You have no problems with **washing and dressing** You have no problems with your **usual activities** You have no **pain or discomfort** You are not **anxious or depressed** You have no problems with the **cosmetic** appearance of your legs.	Immediate Death

CHOICE "B"

100% CHANCE	You will remain in your current state of health

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YOUR CURRENT HEALTH STATE

Please put a tick (✓) against all cases where you are **CONFIDENT** that you would **CHOOSE** the risky treatment in Choice A and an × against all cases where you are **CONFIDENT** that you would **REJECT** the treatment and accept the health state in Choice B.

Please put a "=" against the case where you think it would be most difficult to choose between having the treatment (Choice B).

THE CHANCES IN CHOICE A:

Chance of Success	Chance of Failure	(✓, × or =)
100 in 100	0 in 100	
99 in 100	1 in 100	
98 in 100	2 in 100	
97 in 100	3 in 100	
96 in 100	4 in 100	
95 in 100	5 in 100	
94 in 100	6 in 100	
93 in 100	7 in 100	
92 in 100	8 in 100	
91 in 100	9 in 100	
90 in 100	10 in 100	
80 in 100	20 in 100	
70 in 100	30 in 100	
60 in 100	40 in 100	
50 in 100	50 in 100	
40 in 100	60 in 100	
30 in 100	70 in 100	
20 in 100	80 in 100	
10 in 100	90 in 100	
5 in 100	95 in 100	
0 in 100	100 in 100	

Appendix 3D

One-year follow-up questionnaire

VARICOSE VEIN RESEARCH PROJECT

Patient Questionnaire

1-Year

PART ONE

The following questions ask for your views about your health and how well you are able to do your usual activities.

If you are unsure about how to answer any question, please give the best answer you can and make any comments in the space available after the questionnaire.

1 In general would you say your health is:

Please tick one

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

2 Compared to one year ago, how would you rate your health in general now?

Please tick one

- Much better now than one year ago ☐
- Somewhat better now than one year ago ☐
- About the same ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

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HEALTH AND DAILY ACTIVITIES

4 The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

Please tick one box on each line

		Yes, limited a lot	Yes, limited a little	No, not limited at all	For office use
a.	*Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports.	☐	☐	☐	☐
b.	*Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐	☐
c.	Lifting or carrying groceries	☐	☐	☐	☐
d.	Climbing *several* flights of stairs	☐	☐	☐	☐
e.	Climbing *one* flight of stairs	☐	☐	☐	☐
f.	Bending, kneeling or stooping	☐	☐	☐	☐
g.	Walking *more than a mile*	☐	☐	☐	☐
h.	Walking *half a mile*	☐	☐	☐	☐
i.	Walking *100 yards*	☐	☐	☐	☐
j.	Bathing and dressing yourself	☐	☐	☐	☐

4 During the *past 4 weeks*, have you had any of the following problems with your work or other daily activities *as a result of your physical health*?

Answer Yes or No to each question

		YES	NO	For office use
a.	Cut down on the *amount of time* you spent on work or other activities	☐	☐	☐
b.	*Accomplished less* than you would like	☐	☐	☐
c.	Were limited in the *kind* of work or other activities	☐	☐	☐
d.	Had *difficulty* performing the work or other activities (e.g. it took extra effort)	☐	☐	☐

5 During the *past four weeks*, have you had any of the following problems with your work or other daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

Answer Yes or No to each question

		YES	NO	For office use
a.	Cut down on the *amount of time* you spent on work or other activities	☐	☐	☐
b.	*Accomplished less* than you would like	☐	☐	☐
c.	Didn't do work or other activities as *carefully* as usual	☐	☐	☐

6 During the *past four weeks*, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Please tick one

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7 How much *bodily* pain have you had during the *past 4 weeks*?

Please tick one

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very severe ☐

8 During the *past 4 weeks*, how much did *pain* interfere with your normal work (including work both outside the home and housework)?

Please tick one

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

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YOUR FEELINGS

9 These questions are about how you feel and how things have been with you during the past month. For each question, please indicate the one answer that comes closest to the way you have been feeling.

Please tick one box on each line

How much time during *the past month*

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time	For office use
a.	Did you feel full of life?	☐	☐	☐	☐	☐	☐	☐
b.	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐	☐
c.	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐	☐
d.	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐	☐
e.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐	☐
f.	Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐	☐
g.	Did you feel worn out?	☐	☐	☐	☐	☐	☐	☐
h.	Have you been a happy person?	☐	☐	☐	☐	☐	☐	☐
i.	Did you ever feel tired?	☐	☐	☐	☐	☐	☐	☐

10 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your *social activities* (like visiting friends or close relatives)?

Please tick one

All of the time ☐

Most of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

HEALTH IN GENERAL

11 Please choose the answer that best describes how *true* or *false* each of the following statements is for you.

Please tick one box on each line

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false	
b.	I seem to get ill more easily than other people	☐	☐	☐	☐	☐	☐
b.	I am as healthy as anybody I know	☐	☐	☐	☐	☐	☐
c.	I expect my health to get worse	☐	☐	☐	☐	☐	☐
d.	My health is excellent	☐	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS ASK ABOUT OTHER WAYS IN WHICH THE TROUBLE WITH YOUR VARICOSE VEINS HAS AFFECTED YOU

12 Has your performance of daily activities or your job been limited?

Please tick one

A lot ☐
Moderately ☐
A little ☐
Not at all ☐

13 How long have your varicose veins been causing you problems? _____

14 Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

Please tick one

a) Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

b) Self-care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

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c) Usual Activities

I have no problems with performing my usual activities ☐
(*e.g. work, study, housework, family or leisure activities*)

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

d) Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

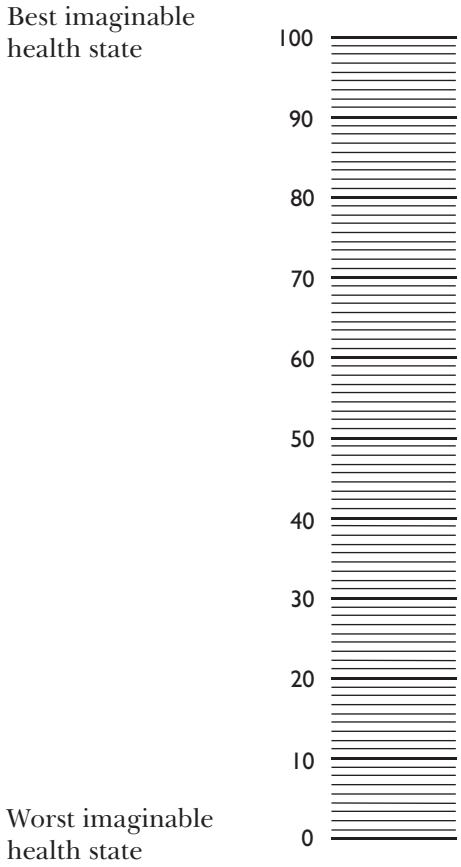
e) Anxiety/Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Please mark the scale on this page to show how you feel your overall health is today



FINALLY, SOME QUESTIONS ABOUT YOURSELF

15 Have you been to see your GP for a problem related to your varicose veins or varicose vein treatment since your last questionnaire (i.e. last six months)?

Yes ☐

No ☐

If yes, how many times? _____

Please give details of the reasons for your visit(s) _____

_____

_____

_____

16 Have you seen any other health professionals (e.g. district nurse) for a problem related to your varicose veins since your last questionnaire

Yes ☐

No ☐

If yes, how many times? _____

Please give details of the reasons for your visit(s) _____

_____

_____

_____

17 Have you attended Accident and Emergency for a problem related to your varicose veins since your last questionnaire?

Yes ☐

No ☐

If yes, how many times? _____

Please give details of the reasons for your visit(s) _____

_____

_____

_____

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18 Are you wearing any support stockings (compression hosiery)?

Yes ☐

No ☐

If "Yes", please give the name or type of stocking _____

19 Compared to your expectations how do you feel about the treatment you received for varicose veins?

Very pleased ☐

Satisfied ☐

Disappointed ☐

Very disappointed ☐

20 Please tick the statement that you most agree with:

My treatment got rid of all my varicose veins (on the leg treated) and problems related to them ☐

My treatment got rid of most of my varicose veins and problems related to them ☐

My treatment got rid of my varicose veins but not the problems related to them ☐

My treatment got rid of none of my varicose veins or symptoms ☐

My veins are still present but not the problems related to them ☐

21 Any other comments you would like to make? .....

.....

.....

.....

.....

Appendix 3E

One-year assessment proforma

HTA VARICOSE VEIN STUDY
1 YEAR CLINICAL ASSESSMENT

Surname: _____ Forename: _____

Hospital Number ☐☐☐☐☐☐☐ Date of Birth ☐☐☐☐☐☐

Consultant _____ Centre: Exeter ◯ Sheffield ◯

Date of assessment: ☐☐☐☐☐☐ Trial Number ☐☐☐☐

Treatment allocated:

Surgery/Sclerotherapy/Conservative/Group 4 (Surgery/Conservative)

Symptoms (since last came to clinic):	**Right**		**Left**	
Aching	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	
Heaviness	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	
Itching	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	
Swelling	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	
Eczema/skin changes	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	
Ulcer	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	
Wearing support hosiery	No ◯	Yes ◯	Yes ◯	No ◯
Cosmetic embarrassment	No ◯	Yes ◯	Yes ◯	No ◯
If "Yes":	Same ◯ Better ◯ Worse ◯		Same ◯ Better ◯ Worse ◯	

Complications (In the last year have you had):				
Phlebitis	Yes ◯	No ◯	Yes ◯	No ◯
Bleeding	Yes ◯	No ◯	Yes ◯	No ◯

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Complications of Treatment

Numbness	Yes ◯	No ◯	Yes ◯	No ◯
Swelling of leg	Yes ◯	No ◯	Yes ◯	No ◯
Thread Veins	Yes ◯	No ◯	Yes ◯	No ◯
Unsightly scars	Yes ◯	No ◯	Yes ◯	No ◯
Skin Staining	Yes ◯	No ◯	Yes ◯	No ◯
VVs not removed	Yes ◯	No ◯	Yes ◯	No ◯
New Varicose Veins	Yes ◯	No ◯	Yes ◯	No ◯
Other	Yes ◯	No ◯	Yes ◯	No ◯

Medical History Since Last Visit

		Comments
Heart problems	◯	
Breathing problems	◯	
Allergies	◯	
Previous pregnancies	◯	

Medication:

Contraceptive pill Yes ◯ No ◯ HRT Yes ◯ No ◯

Height (cm) ☐☐☐ Weight ☐☐☐

BMI ☐☐

Examination

Assessor (initials) ☐

Clinical:	**Right**			**Left**		
Varicose veins in upper 1/3 thigh?	Yes ◯	No ◯		Yes ◯	No ◯	
	<5 mm ◯	◯ >5 mm	◯ none	<5 mm ◯	◯ >5 mm	◯ none
Varicose veins in lower 2/3 thigh?	Yes ◯	No ◯		Yes ◯	No ◯	
	<5 mm ◯	◯ >5 mm	◯ none	<5 mm ◯	◯ >5 mm	◯ none
Below knee varicose veins?	Yes ◯	No ◯		Yes ◯	No ◯	
	<5 mm ◯	◯ >5 mm	◯ none	<5 mm ◯	◯ >5 mm	◯ none
Extent (number of quadrants)		☐			☐	

Treatment

	Right	**Left**
Result		
No Varicose Veins	○	○
Few Varicose Veins	○	○
No change	○	○

Comments

Needs Further Appointment Yes ○ No ○

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Appendix 4

Alternative cost-effectiveness analyses

TABLE 78 *Summary of outcome and NHS costs using EQ-5D*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Mean NHS cost over 24 months (discounted) (£)[a]	296.04 (356.07) *n* = 31	675.94 (248.65) *n* = 19	–379.89	–566.62 to –193.17
Mean NHS cost over 24 months (discounted) (£)[a,b]	325.52 (355.70) *n* = 54	764.27 (367.36) *n* = 37	–438.76	–591.61 to –285.90
Area under the curve EQ-5D, 0 to 24 months (discounted)	1.662 (0.209) *n* = 31	1.748 (0.223) *n* = 19	–0.086	–0.224 to 0.052
Area under the curve EQ-5D, 0 to 24 months (discounted)[a,b]	1.615 (0.299) *n* = 54	1.748 (0.242) *n* = 37	–0.133	–0.251 to 0.016
ICER (£)[c]			4417 3299[b]	1868 to 21,561 1785 to 20,157

[a] Significant difference of means at the 5% level.
[b] Imputed data for missing EQ-5D values using straight-line interpolation.
[c] 95% CI estimated using the 5th and 95th percentiles of the bootstrap repetition ICER values.

TABLE 79 *Summary of outcome and NHS costs using mean NHS reference unit cost rather than local unit cost for surgical treatment*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Mean NHS cost over 24 months (discounted) (£)[a]	414.71 (461.16) *n* = 31	888.80 (222.11) *n* = 20	–474.10	–668.48 to –279.70
Mean NHS cost over 24 months (discounted) (£)[a,b]	437.13 (458.22) *n* = 53	910.90 (160.49) *n* = 41	–473.77	–622.64 to –324.91
Area under the curve SF-6D, 0 to 24 months (discounted)	1.443 (0.209) *n* = 31	1.498 (0.192) *n* = 20	–0.054	–0.171 to 0.062
Area under the curve SF-6D, 0 to 24 months (discounted)[a,b]	1.420 (0.205) *n* = 53	1.503 (0.168) *n* = 41	–0.083	–0.162 to –0.005
ICER (£)[c]			£8780 £5708[b]	4621 to 23,739 2726 to 22,264

[a] Significant difference of means at the 5% level.
[b] Imputed data for missing SF-6D values using straight-line interpolation.
[c] 95% confidence interval estimated using the 5th and 95th percentiles of the bootstrap repetition ICER values.

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TABLE 80 *Summary of outcome and NHS costs using lower quartile of NHS reference unit cost rather than local unit cost for surgical treatment*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Mean NHS cost over 24 months (discounted) (£)[a]	328.10 (360.87) *n* = 31	544.54 (148.56) *n* = 20	–216.45	–387.70 to –45.19
Mean NHS cost over 24 months (discounted) (£)[a,b]	344.53 (357.47) *n* = 53	557.49 (111.74) *n* = 41	–212.96	–328.07 to –97.85
Area under the curve SF-6D, 0 to 24 months (discounted)	1.443 (0.209) *n* = 31	1.498 (0.192) *n* = 20	–0.054	–0.171 to 0.062
Area under the curve SF-6D, 0 to 24 months (discounted)[a,b]	1.420 (0.205) *n* = 53	1.503 (0.168) *n* = 41	–0.083	–0.162 to –0.005
ICER (£)[c]			4008 2566[b]	2914 to 21,624 1298 to 18,285

[a] Significant difference of means at the 5% level.
[b] Imputed data for missing SF-6D values using straight-line interpolation.
[c] 95% CI estimated using the 5th and 95th percentiles of the bootstrap repetition ICER values.

TABLE 81 *Summary of outcome and NHS costs using upper quartile of NHS reference unit cost rather than local unit cost for surgical treatment*

	Conservative: mean (SD)	Surgery: mean (SD)	Difference in means	95% CI
Mean NHS cost over 24 months (discounted) (£)[a]	328.10 (360.87) *n* = 31	855.19 (214.20) *n* = 20	–527.10	–707.09 to –347.11
Mean NHS cost over 24 months (discounted) (£)[a,b]	344.53 (357.47) *n* = 53	1388.71 (231.51) *n* = 41	–1044.18	–1171.86 to –916.51
Area under the curve SF-6D, 0 to 24 months (discounted)	1.443 (0.209) *n* = 31	1.498 (0.192) *n* = 20	–0.054	–0.171 to 0.062
Area under the curve SF-6D, 0 to 24 months (discounted)[a,b]	1.420 (0.205) *n* = 53	1.503 (0.168) *n* = 41	–0.083	–0.162 to –0.005
ICER (£)[c]			9761 12,580[a]	4914 to 25,624 7826 to 27,410

[a] Significant difference of means at the 5% level.
[b] Imputed data for missing SF-6D values using straight-line interpolation.
[c] 95% confidence interval estimated using the 5th and 95th percentiles of the bootstrap repetition ICER values.

Appendix 5

Willingness to pay questionnaire

Eliciting patient preferences for alternative treatments for varicose veins using the willingness to pay technique

PARTICIPANT QUESTIONNAIRE

PLEASE COMPLETE THIS QUESTIONNAIRE AND RETURN IN THE ENCLOSED PRE-PAID ENVELOPE

Thank you for your help with our research project

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REACTIV WTP exercise

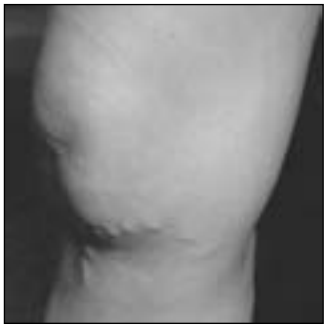
SECTION 1

IMPORTANT

The following questions ask you to imagine that you have varicose veins symptoms which may be different from those you are actually experiencing. It is important for the purposes of the questionnaire that you focus on the symptoms in the description rather than your own symptoms.

Please <u>imagine</u> that you are experiencing the following varicose veins symptoms:

- You have some small varicose veins mostly below the knee, and a few tiny ones in the lower part of your thigh.
- Your veins hardly ever cause any symptoms, but may give you an occasional mild ache.
- Your veins are not particularly noticeable, and their appearance does not bother you much at all.
- You have never had any skin trouble on your leg caused by varicose veins, and you will almost certainly never have any in the future.
- You have no special risk of developing deep vein thrombosis as a result of your varicose veins, nor are they ever likely to cause bleeding.



Treatment Options – Conservative Treatment and Injection Treatment

Conservative Treatment	Injection Treatment
What this treatment involves: ⇒ Losing weight by dieting and exercise ⇒ Regular exercise, such as walking, jogging, running, cycling, swimming, or other sports ⇒ Elevation – putting your feet up at the end of the day can relieve discomfort due to varicose veins ⇒ You are recommended to wear support stockings or tights. These can be light weight support tights which you buy for yourself, or stronger support stockings prescribed by your doctor ⇒ Conservative treatment is almost all done at home, as part of your daily routine ⇒ Getting advice about weight loss may mean visiting a dietician at the hospital or the health centre. Prescription of support stockings means a visit to your family doctor	**What this treatment involves:** ⇒ Injection treatment involves injection of a chemical substance into varicose veins which glues their walls together and causes them to close off and disappear ⇒ A doctor gives you one or more injections into the varicose veins using a small needle. Other than a 'pinprick' the injections usually cause no pain ⇒ Each injected area is covered with a soft pad, and a bandage and/or a compression stocking is then applied, to compress the veins and help them to seal off ⇒ The bandage and/or stocking needs to be worn continuously for 2–3 weeks
Where this treatment takes place: Conservative treatment is almost all done at home, as part of your daily routine.	**Where this treatment takes place:** Injection treatment is given at the hospital outpatient department.

continued

What are the results of this treatment?	**What are the results of this treatment?**
Time off work ⇒ Conservative treatment involves no time off work	**Time off work** Injection treatment usually means no more than a day off work
Risks ⇒ There are no special risks of conservative treatment	**Risks** ⇒ Occasionally inflammation of the injected veins can cause pain and throbbing, which may require painkillers for a few days ⇒ The injected areas sometimes feel hard for several weeks, and may be tender for the first week or two after the bandage/stocking is removed ⇒ Sometimes there is a 50% chance of brown staining of the skin in the areas which were injected, which will be permanent ⇒ Very occasionally tiny blue thread veins can appear in injected areas and exceptionally skin damage by the injection can leave a small scar ⇒ Deep vein thrombosis is a risk, but is very rare
Outcome ⇒ Conservative treatment aims to relieve symptoms of varicose veins but none of the veins will go away. ⇒ You have a 50% chance of developing more varicose veins as the years go by ⇒ Varicose veins can become more widespread during pregnancy	**Outcome** ⇒ The injections should get rid of all the varicose veins injected but there is no guarantee that any symptoms you get from them will go away ⇒ More varicose veins may develop in the future. You have a 50% chance in the next 5 years of your veins coming back much as they were before treatment

Questions

If **you** were experiencing the symptoms in the description, which treatment would you prefer to receive?

Conservative treatment	☐	If you ticked this box, please go to the Conservative treatment question below
Injection sclerotherapy	☐	If you ticked this box, please go to the Sclerotherapy question
Prefer both equally	☐	If you ticked this box, please go to SECTION 2

CONSERVATIVE TREATMENT
Question A

One way of measuring the value to you of conservative treatment is to ask you how much (if anything) you would be prepared to pay to receive this treatment rather than injection sclerotherapy. Of course, there is no question of you actually having to pay. This study is not about setting charges for health care. It is just a hypothetical exercise in which you are asked to **imagine** that you have to pay. We use the technique of 'willingness to pay' simply because it allows us to gauge how strongly people feel about their health care preferences. One way to think of this is to imagine you are at an auction at which the most you would pay for an item shows the importance you place on that item. How far are you prepared to go?

Please remember, there are no right or wrong answers. The amount you say could be large or small. We are interested in your view.

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What is the maximum amount of money you would be prepared to pay to receive conservative treatment rather than injection sclerotherapy?

	£0	
	£5	Please tick (✓) the amounts you are sure you
	£10	would pay
	£20	
	£50	
You do not have	£75	Please put a cross (✕) next to the amounts you
to mark every	£100	are sure you would not pay
amount on the list	£150	
	£200	
	£300	
	£400	Please put a circle (◯) around the maximum
	£500	amount you would be willing to pay
	£1000	
	£2000	
	£3000	
	£4000	
	£5000	

If your value is not on the list, or is more than £5000, please write in the exact amount £ ……..

Now please go to Question B

SCLEROTHERAPY
Question A

One way of measuring the value to you of injection sclerotherapy is to ask you how much (if anything) you would be prepared to pay to receive this treatment rather than conservative treatment. Of course, there is no question of you actually having to pay. This study is not about setting charges for health care. It is just a hypothetical exercise in which you are asked to imagine that you have to pay. We use the technique of 'willingness to pay' simply because it allows us to gauge how strongly people feel about their health care preferences. One way to think of this is to imagine you are at an auction at which the most you would pay for an item shows the importance you place on that item. How far are you prepared to go?

Please remember, there are no right or wrong answers. The amount you say could be large or small. We are interested in your view.

What is the maximum amount of money you would be prepared to pay to receive injection sclerotherapy rather than conservative treatment?

	£0	
	£5	Please tick (✓) the amounts you are sure you
	£10	would pay
	£20	
	£50	
You do not have	£75	Please put a cross (×) next to the amounts you
to mark every	£100	are sure you would not pay
amount on the list	£150	
	£200	
	£300	
	£400	Please put a circle (◯) around the maximum
	£500	amount you would be willing to pay
	£1000	
	£2000	
	£3000	
	£4000	
	£5000	

If your value is not on the list, or is more than £5000, please write in the exact amount £ ……..

Now please go to Question B

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Question B

Could you please write in the space below the reasons why you were willing to pay the amount you indicated for your preferred treatment? If you were not willing to pay anything, please state why.

PLEASE NOW GO TO SECTION 2

REACTIV WTP exercise

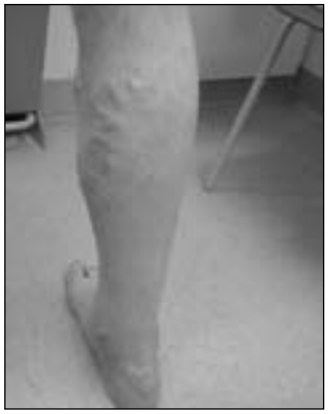
SECTION 2

IMPORTANT

The following questions ask you to imagine that you have varicose vein symptoms which may be different from those you are actually experiencing. It is important for the purposes of the questionnaire that you focus on the symptoms in the description rather than your own symptoms.

Please <u>imagine</u> that you are experiencing the following varicose veins symptoms:

- You have a few small varicose veins in the lower part of your thigh, and some larger ones in just one area of your leg below the knee.
- Your veins cause some aching in hot weather or if you have been on your feet for a long time.
- They itch occasionally.
- You have never had any skin trouble on your leg caused by varicose veins, and you will almost certainly never have any in the future.
- You have no special risk of developing deep vein thrombosis as a result of your varicose veins, nor are they ever likely to cause bleeding.



Treatment Options – Surgical Treatment and Injection Treatment

Surgical Treatment	Injection Treatment
What this treatment involves: ⇒ You will need a general anaesthetic ⇒ You will need a surgical operation which removes (strips) the varicose veins and ties off where the valves in the veins have been leaking ⇒ An incision about 5 cm long is made in the groin, and a number of much smaller incisions (mostly about 3 mm) over the varicose veins ⇒ The incisions are closed with stitches under the skin or adhesive strips – no stitches need to be removed (they dissolve)	**What this treatment involves:** ⇒ Injection treatment involves injection of a chemical substance into varicose veins which glues their walls together and causes them to close off and disappear ⇒ A doctor gives you one or more injections into the varicose veins using a small needle. Other than a 'pinprick' the injections usually cause no pain ⇒ Each injected area is covered with a soft pad, and a bandage and/or a compression stocking is then applied, to compress the veins and help them to seal off ⇒ The bandage and/or stocking needs to be worn continuously for 2–3 weeks
Where this treatment takes place: Surgery is usually performed as a day case but you may need to stay overnight in hospital	**Where this treatment takes place:** Injection treatment is given at the hospital outpatient department
What are the results of this treatment? **Time off work** You can get back to work as soon as you are comfortable. However, many people with an 'office job' are off work for a week or so, and people with physically very active jobs may be off work for 2–3 weeks	**What are the results of this treatment?** **Time off work** Injection treatment usually means no more than a day off work

continued

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Risks ⇒ There is a very small risk of serious complications with any general anaesthetic ⇒ Damage to small nerves under the skin can result in areas of numbness (which may or may not recover) and affect about one in five (20%) of patients ⇒ Infection can occasionally occur, particularly in the groin, and is treated with antibiotics, and occasionally by opening the wound and dressing it ⇒ Deep vein thrombosis is a risk, but this is uncommon (about 1%)	**Risks** ⇒ Occasionally inflammation of the injected veins can cause pain and throbbing, which may require painkillers for a few days ⇒ The injected areas sometimes feel hard for several weeks, and may be tender for the first week or two after the bandage/stocking is removed ⇒ Sometimes there is a 50% chance of brown staining of the skin in the areas which were injected, which will be permanent ⇒ Very occasionally tiny blue thread veins can appear in injected areas and exceptionally skin damage by the injection can leave a small scar ⇒ Deep vein thrombosis is a risk, but is very rare
Outcome ⇒ The surgery should get rid of all the varicose veins but there is no guarantee that any symptoms you get from them will go away ⇒ More varicose veins may develop in the future. You have a 25% chance in the next 5 years of your veins coming back much as they were before treatment	**Outcome** ⇒ The injections should get rid of all the varicose veins injected but there is no guarantee that any symptoms you get from them will go away ⇒ More varicose veins may develop in the future. You have a 50% chance in the next 5 years of your veins coming back much as they were before treatment

Questions

1. If **you** were experiencing the symptoms in the description, which treatment would you prefer to receive?

Surgery	☐	If you ticked this box, please go to the Surgery question below
Injection sclerotherapy	☐	If you ticked this box, please go to the Sclerotherapy question below
Prefer both equally	☐	If you ticked this box, please go to SECTION 3

SURGERY
Question A

One way of measuring the value to you of surgery treatment is to ask you how much (if anything) you would be prepared to pay to receive this treatment rather than injection sclerotherapy. Of course, there is no question of you actually having to pay. This study is not about setting charges for health care. It is just a hypothetical exercise in which you are asked to **imagine** that you have to pay. We use the technique of 'willingness to pay' simply because it allows us to gauge how strongly people feel about their health care preferences. One way to think of this is to imagine you are at an auction at which the most you would pay for an item shows the importance you place on that item. How far are you prepared to go?

Please remember, there are no right or wrong answers. The amount you say could be large or small. We are interested in your view.

What is the maximum amount of money you would be prepared to pay to receive surgery rather than injection sclerotherapy?

	£0	
	£5	Please tick (✓) the amounts you are sure you
	£10	would pay
	£20	
	£50	
You do not have	£75	Please put a cross (×) next to the amounts you
to mark every	£100	are sure you would not pay
amount on the list	£150	
	£200	
	£300	
	£400	Please put a circle (◯) around the maximum
	£500	amount you would be willing to pay
	£1000	
	£2000	
	£3000	
	£4000	
	£5000	

If your value is not on the list, or is more than £5000, please write in the exact amount £ ……..

Now please go to Question B

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SCLEROTHERAPY
Question A

One way of measuring the value to you of injection sclerotherapy is to ask you how much (if anything) you would be prepared to pay to receive this treatment rather than surgery. Of course, there is no question of you actually having to pay. This study is not about setting charges for health care. It is just a hypothetical exercise in which you are asked to imagine that you have to pay. We use the technique of 'willingness to pay' simply because it allows us to gauge how strongly people feel about their health care preferences. One way to think of this is to imagine you are at an auction at which the most you would pay for an item shows the importance you place on that item. How far are you prepared to go?

Please remember, there are no right or wrong answers. The amount you say could be large or small. We are interested in your view.

What is the maximum amount of money you would be prepared to pay to receive injection sclerotherapy rather than surgery?

	£0	
	£5	Please tick (✓) the amounts you are sure you
	£10	would pay
	£20	
	£50	
You do not have	£75	Please put a cross (✕) next to the amounts you
to mark every	£100	are sure you would not pay
amount on the list	£150	
	£200	
	£300	
	£400	Please put a circle (◯) around the maximum
	£500	amount you would be willing to pay
	£1000	
	£2000	
	£3000	
	£4000	
	£5000	

If your value is not on the list, or is more than £5000, please write in the exact amount £……..

Now please go to Question B

Question B

Could you please write in the space below the reasons why you were willing to pay the amount you indicated for your preferred treatment? If you were not willing to pay anything, please state why.

PLEASE NOW GO TO SECTION 3

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REACTIV WTP exercise

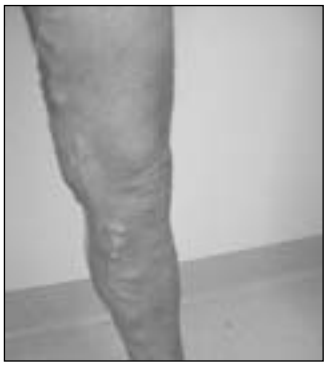
SECTION 3

IMPORTANT

The following questions ask you to imagine that you have varicose veins symptoms which may be different from those you are actually experiencing. It is important for the purposes of the questionnaire that you focus on the symptoms in the description rather than your own symptoms.

Please imagine that you are experiencing the following varicose veins symptoms:

- You have quite large varicose veins both in your thigh and affecting a large area of your leg below the knee as well.
- Your veins cause some aching most days, and your leg feels heavy especially in hot weather or if you have been on your feet for a long time. Your veins itch as well.
- Your ankle and lower leg sometimes swell a little, especially in hot weather or when you have been on your feet for a long time.
- You have never had any skin trouble on your leg due to varicose veins. There is a small chance that you might develop darkening of the skin or eczema as the years go by, but you are unlikely ever to get an ulcer.



Treatment Options – Surgical Treatment and Conservative Treatment:

Surgical Treatment	Conservative Treatment
What this treatment involves: ⇒ You will need a general anaesthetic ⇒ You will need a surgical operation which removes (strips) the varicose veins and ties off where the valves in the veins have been leaking ⇒ An incision about 5 cm long is made in the groin, and a number of much smaller incisions (mostly about 3 mm) over the varicose veins ⇒ The incisions are closed with stitches under the skin or adhesive strips – no stitches need to be removed (they dissolve)	**What this treatment involves:** ⇒ Losing weight by dieting and exercise ⇒ Regular exercise, such as walking, jogging, running, cycling, swimming or other sports ⇒ Elevation – putting your feet up at the end of the day can relieve discomfort due to varicose veins ⇒ You are recommended to wear support stockings or tights. These can be light weight support tights which you buy for yourself, or stronger support stockings prescribed by your doctor ⇒ Conservative treatment is almost all done at home, as part of your daily routine ⇒ Getting advice about weight loss may mean visiting a dietician at the hospital or the health centre. Prescription of support stockings means a visit to your family doctor
Where this treatment takes place: Surgery is usually performed as a day case but you may need to stay overnight in hospital	**Where this treatment takes place:** Conservative treatment is almost all done at home, as part of your daily routine
What are the results of this treatment?	**What are the results of this treatment?**
Time off work You can get back to work as soon as you are comfortable. However, many people with an 'office job' are off work for a week or so, and people with physically very active jobs may be off work for 2–3 weeks	**Time off work** ⇒ Conservative treatment involves no time off work

continued

Risks ⇒ There is a very small risk of serious complications with any general anaesthetic ⇒ Damage to small nerves under the skin can result in areas of numbness (which may or may not recover) and affect about one in five (20%) of patients ⇒ Infection can occasionally occur, particularly in the groin and is treated with antibiotics, and occasionally by opening the wound and dressing it ⇒ Deep vein thrombosis is a risk, but this is uncommon (about 1%)	**Risks** ⇒ There are no special risks of conservative treatment
Outcome ⇒ The surgery should get rid of all the varicose veins but there is no guarantee that any symptoms you get from them will go away ⇒ More varicose veins may develop in the future. You have a 25% chance in the next 5 years of your veins coming back as much as they were before treatment	**Outcome** ⇒ Conservative treatment aims to relieve symptoms of varicose veins but none of the veins will go away ⇒ You have a 50% chance of developing more varicose veins as the years go by ⇒ Varicose veins can become more widespread during pregnancy

Questions

1. If **you** were experiencing the symptoms in the description, which treatment would you prefer to receive?

Surgery	☐	If you ticked this box, please go to the Surgery question below
Conservative treatment	☐	If you ticked this box, please go to the Conservative treatment question
Prefer both equally	☐	If you ticked this box, please go to the 'About yourself' section

SURGERY
Question A

One way of measuring the value to you of surgery treatment is to ask you how much (if anything) you would be prepared to pay to receive this treatment rather than conservative treatment. Of course, there is no question of you actually having to pay. This study is not about setting charges for health care. It is just a hypothetical exercise in which you are asked to **imagine** that you have to pay. We use the technique of 'willingness to pay' simply because it allows us to gauge how strongly people feel about their health care preferences. One way to think of this is to imagine you are at an auction at which the most you would pay for an item shows the importance you place on that item. How far are you prepared to go?

Please remember, there are no right or wrong answers. The amount you say could be large or small. We are interested in your view.

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What is the maximum amount of money you would be prepared to pay to receive surgery rather than conservative treatment?

	£0	
	£5	Please tick (✓) the amounts you are sure you
	£10	would pay
	£20	
	£50	
You do not have	£75	Please put a cross (✕) next to the amounts you
to mark every	£100	are sure you would not pay
amount on the list	£150	
	£200	
	£300	
	£400	Please put a circle (◯) around the maximum
	£500	amount you would be willing to pay
	£1000	
	£2000	
	£3000	
	£4000	
	£5000	

If your value is not on the list, or is more than £5000, please write in the exact amount £ ……..

Now please go to Question B

CONSERVATIVE TREATMENT
Question A

One way of measuring the value to you of conservative treatment is to ask you how much (if anything) you would be prepared to pay to receive this treatment rather than surgery. Of course, there is no question of you actually having to pay. This study is not about setting charges for health care. It is just a hypothetical exercise in which you are asked to imagine that you have to pay. We use the technique of 'willingness to pay' simply because it allows us to gauge how strongly people feel about their health care preferences. One way to think of this is to imagine you are at an auction at which the most you would pay for an item shows the importance you place on that item. How far are you prepared to go?

Please remember, there are no right or wrong answers. The amount you say could be large or small. We are interested in your view.

What is the maximum amount of money you would be prepared to pay to receive conservative treatment rather than surgery?

	£0	
	£5	Please tick (✓) the amounts you are sure you
	£10	would pay
	£20	
	£50	
You do not have	£75	Please put a cross (×) next to the amounts you
to mark every	£100	are sure you would not pay
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	£500	amount you would be willing to pay
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	£5000	

If your value is not on the list, or is more than £5000, please write in the exact amount £ ……..

Now please go to Question B

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Question B

Could you please write in the space below the reasons why you were willing to pay the amount you indicated for your preferred treatment? If you were not willing to pay anything, please state why.

Now please go to the 'About yourself' section

About Yourself

1. How old are you? _____ years

2. Please indicate your sex:

   Male ☐
   Female ☐

3. Have you previously received treatment for varicose veins?

   Yes ☐
   No ☐

4. If yes, please give details below.

5. What is your occupation?

   _____

6. How many dependent children do you have?

   _____

7. What is your highest level of education?

   Primary ☐
   Secondary (O-level/GCSE) ☐
   A-level ☐
   University ☐
   Other (please specify below) ☐

   _____

8. In general, would you say your health is:

   Excellent ☐
   Very good ☐
   Good ☐
   Fair ☐
   Poor ☐

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9. Could you please indicate your annual income before deducting tax and national insurance? (If you receive any benefits or pensions, include them as income.)

Less than £5,000	☐
£5,000–£9,999	☐
£10,000–£14,999	☐
£15,000–£19,999	☐
£20,000–£24,999	☐
£25,000–£30,000	☐
More than £30,000	☐

We would like to remind you that the results of this study will not be used for charging for services. The results will be used for research purposes only

Please return your completed questionnaire in the enclosed stamped addressed envelope

Many thanks for your valuable contribution to this study

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The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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