OUTCOMES FROM ULTRASOUND-GUIDED FOAM SCLEROTHERAPY FOR CHRONIC VENOUS DISEASE

by

KATY ABIGAIL LEIGH DARVALL

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Department of Surgery
School of Medicine
The University of Birmingham

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ABSTRACT

The objective of this research is to investigate the role of ultrasound-guided foam sclerotherapy (UGFS) in the treatment of chronic venous disease (CVD).

UGFS was found to be a safe and effective treatment for both primary and recurrent great saphenous vein (GSV) and small saphenous vein (SSV) incompetence, assessed by occlusion of treated veins on duplex ultrasound (DUS), and by disappearance of visible varicose veins (VV) on clinical examination. There was some evidence that healing of chronic venous ulcers (CVU) may be improved by UGFS when combined with compression bandaging.

When compared with patients undergoing superficial venous surgery (SVS), UGFS was associated with significantly less pain, bruising and analgesia requirement, and a quicker return to work and driving.

Significant improvements in both generic physical and disease-specific health-related quality of life (HRQL) were observed following UGFS, and were sustained for 12 months after treatment. UGFS significantly improved lower limb physical symptoms (pain, itching, restlessness, swelling, heaviness, cramp and tingling), cosmetic appearance, and provided life-style benefits in the majority of patients. Furthermore, the great majority of patients who expected such benefits had their expectations met or exceeded.

Dedicated to Elliott and Imogen Darvall

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LIST OF ABBREVIATIONS

AASV	Anterior accessory saphenous vein
ABPI	Ankle-brachial pressure index
AVSS	Aberdeen Varicose Vein Symptom Severity Score
CEAP	Clinical (A)Etiological Anatomical Pathophysiological classification system for chronic venous disease
CVD	Chronic venous disease
CVI	Chronic venous insufficiency
CVU	Chronic venous ulceration
DUS	Duplex ultrasonography
DVR	Deep venous reflux
DVT	Deep vein thrombosis
EVLA	Endovenous laser ablation
GSV	Great saphenous vein
GSVV	Great saphenous varicose veins
HRQL	Health-related quality of life
IQR	Interquartile range
MCS	Mental component summary

NHS	National Health Service
PCS	Physical component summary
PE	Pulmonary embolism
PFO	Patent foramen ovale
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
SF12	Short Form-12
SF36	Short Form-36
SFJ	Sapheno-femoral junction
SPJ	Sapheno-popliteal junction
SSV	Small saphenous vein
SSVV	Small saphenous varicose veins
STS	Sodium tetradecyl sulphate
SVR	Superficial venous reflux
SVS	Superficial venous surgery
UGFS	Ultrasound-guided foam sclerotherapy
VV	Varicose veins

CHAPTER 1. INTRODUCTION

1.1 Classification of chronic venous disease

Chronic venous disease (CVD) can affect either the deep or superficial venous systems, resulting in a wide range of clinical conditions: varicose veins (VV), chronic venous insufficiency (CVI), and chronic venous ulceration (CVU). Many classification systems have been developed for CVD, but the most widely used, and the one I have used throughout this Thesis, is the CEAP classification (**Table 1.1**). (Eklof *et al*., 2004)

There are four parts to the classification: clinical severity (C), aetiology (E), anatomical distribution (A) and pathophysiology (P). The clinical classification ranges in severity from C_0 where there are no palpable or visible signs of venous disease to C_6 where there is active CVU present; this is suffixed by 's' or 'a' according to whether the limb is symptomatic or asymptomatic. Aetiology can be congenital (E_c), primary (E_p) or secondary (E_s). Anatomical distribution, which is determined by imaging, can be superficial (A_s), deep (A_d), or from the perforating veins (A_p), or a combination. The pathophysiology of the disease may be reflux (P_r) or obstruction (P_o). In this Thesis I am concerned with the management of patients with symptomatic, CEAP clinical grades $C_{2\text{-}6}$ CVD, all of primary aetiology, all with superficial venous reflux (SVR) with or without deep venous reflux (DVR), and all with reflux rather than obstruction. VV without evidence of skin changes of CVI (pigmentation, eczema, lipodermatosclerosis) will at times be referred to as 'uncomplicated VV' ($C_{2\text{-}3}$) and those with skin changes of CVI as 'complicated VV' ($C_{4\text{-}6}$).

Table 1.1 Basic CEAP classification

Classification	
Clinical classification	
C_0	No visible or palpable signs of venous disease
C_1	Telangiectases or reticular veins
C_2	Varicose veins
C_3	Oedema
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
A(E)tiologic classification	
E_c	Congenital
E_p	Primary
E_s	Secondary (post-thrombotic)
E_n	No venous cause identified
Anatomic classification	
A_s	Superficial veins
A_p	Perforator veins
A_d	Deep veins
A_n	No venous location identified
Pathophysiologic classification	
P_r	Reflux
P_o	Obstruction
$P_{r,o}$	Reflux and obstruction
P_n	No venous pathophysiology identifiable

1.2 Reasons for seeking treatment

When assessing a patient for treatment, it is important to establish what has prompted the patient to seek medical attention for their CVD. For example, many patients with asymptomatic and uncomplicated VV may be simply concerned about

their future risk of ulceration and thrombosis and may be reassured. Others are primarily concerned about the appearance of their legs, while some wish to have physical symptoms such as aching and itching relieved. Yet others seek treatment for the skin complications of CVI. Failure to understand, and therefore meet, the patient's expectations are likely to be an important cause of dissatisfaction, complaint and even medico-legal action. (Jackson and Kroenke, 2001; Kravitz, 2001; Campbell and France, 2002)

1.2.1 Appearance

Many patients who seek treatment for their VV are concerned about the appearance of their legs and related 'lifestyle' issues, but these may not be their only, or even their predominant concerns. Most patients are aware that they are unlikely to get treatment for VV for cosmetic indications within a publicly-funded health system such as the National Health Service (NHS), (especially at a time when significant reductions on healthcare spending are being sought), and thus may invent, or at least inflate, concerns about physical symptoms.

1.2.2 Lower limb symptoms

A wide range of lower limb symptoms have been ascribed to CVD: most commonly pain, heaviness, swelling, itching, restlessness and cramps. Symptoms tend to be less troublesome in the mornings, increase over the course of the day or with

prolonged periods of standing and are often ameliorated by the use of support hosiery.

Clinical experience indicates that there are large numbers of people with significant CVD who are asymptomatic, while other patients with apparently trivial disease seem to be greatly troubled by their legs. This often poor relationship between the symptoms of CVD, the signs on clinical examination, and the results of investigations, has been noted in a number of clinical and population-based studies. (Bradbury *et al*., 1999; Bradbury *et al*., 2000) These observations lead to the assumption that some patients with uncomplicated VV with marked symptoms, who may currently be denied treatment on the NHS in some geographical areas of the United Kingdom (UK), have a lot to gain from treatment in terms of improvement in both symptoms and possibly health-related quality of life (HRQL), and this is an area ripe for study.

1.2.3 Skin complications of chronic venous insufficiency

There is some evidence that eradicating SVR may improve, or at least prevent progression of, the skin changes of CVI. The mainstay of treatment for CVU is elastic, multi-layer graduated bandaging followed by knee-length European class II compression hosiery. (Fletcher *et al*., 1997; Palfreyman *et al*., 1998; Cullum *et al*., 2001) In terms of CVU management however, it is widely agreed that eradication of SVR, traditionally by superficial venous surgery (SVS), is effective in reducing recurrence following ulcer healing, but does not significantly accelerate ulcer healing itself. (Barwell *et al*., 2004) Only one study has found improved CVU healing rates

following SVS, but this was only true in patients with isolated saphenous reflux. (Scriven *et al*., 1998)

1.3 Current treatment of superficial venous reflux

The perfect treatment for VV would rapidly and permanently abolish all sources of SVR, relieve all physical symptoms, significantly improve the appearance of the leg, be complication-free, allow a fast (immediate) return to normal activities, be inexpensive, and be widely available and applicable to affected patients. (Beale and Gough, 2005) Such treatment does not and probably will never exist, but well aware of the shortcomings of SVS, clinicians have devoted considerable energies to the development of minimally-invasive alternatives, such as radiofrequency ablation (RFA), endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS).

1.3.1 Superficial venous surgery

SVS that aims to remove visible VV and correct axial superficial and perforator (deep to superficial) incompetence has been considered the 'gold standard' for many decades. In patients with great saphenous vein (GSV) incompetence, the sapheno-femoral junction (SFJ) is ligated and the GSV is stripped out from the groin to the knee. Recurrence is much less likely when the GSV is adequately stripped. (Dwerryhouse *et al*., 1999; MacKenzie *et al*., 2002b) In patients with small saphenous vein (SSV) incompetence the sapheno-popliteal junction (SPJ) is ligated.

Many surgeons do not strip the SSV, often because of fear of damage to the sural nerve, but may remove a short portion of the proximal vein. (Sam *et al*., 2004b; Winterborn *et al*., 2004) Any remaining varices are removed through several tiny stab incisions (avulsions). In the UK, SVS is usually performed under general anaesthesia and many people take at least two weeks away from work.

In most patients SVS results in relief of symptoms and improvement in both generic and disease-specific HRQL. (O'Shaughnessy *et al*., 1989; Baker *et al*., 1995; Smith *et al*., 1999; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam *et al*., 2004a) However, around one quarter of patients are dissatisfied with their treatment at five to ten year follow-up. (O'Shaughnessy *et al*., 1989; Davies *et al*., 1995) Recurrence is common with reflux demonstrated on duplex ultrasound (DUS) in 13-29% of patients at two to five years, (Jones *et al*., 1996; Dwerryhouse *et al*., 1999; Turton *et al*., 1999; Van Rij *et al*., 2003) and clinical recurrence in up to 37% of patients. (Dwerryhouse *et al*., 1999; Jones *et al*., 1996) SVS is also one of the most common areas for litigation in the UK and, although usually considered fairly minor surgery, carries with it risks of wound infection or haematoma, thrombo-embolism and cutaneous nerve injury. (Corder *et al*., 1991; Hayden and Holdsworth, 2001; Sam *et al*., 2004b; Van Rij *et al*., 2004)

1.3.2 Radiofrequency ablation

RFA was developed as an 'office-based' procedure as an alternative to SVS with the aims of reducing post-operative pain and bruising, avoiding the need for an incision

in the groin, allowing earlier return to mobility and thus to work, and delivering a better cosmetic result.

The VNUS Closure® system was introduced in 1998 by VNUS Medical technologies (California, USA; now owned by Covidien) for ablation of the GSV using a radiofrequency current, and more recently Celon AG (Berlin, Germany) have introduced RFITT® (radiofrequency-induced thermo-therapy; now owned by Olympus). RFA is usually performed using local (tumescent) anaesthesia. The treated vein is obliterated by a combination of denaturation of collagen fibres in the vein wall and thrombus formation. (Subramonia and Lees, 2007)

Early results show complete occlusion of treated veins in over 90% of cases, and 85-100% occlusion at two-year follow-up. (Weiss and Weiss, 2002; Lurie *et al*., 2003; Pichot *et al*., 2004; Lurie *et al*., 2005; Merchant *et al*., 2005) Reported complications include paraesthesia, skin burns, haematomas and phlebitis, with symptomatic deep vein thrombosis (DVT) occurring in around 1% of patients undergoing RFA. (Weiss and Weiss, 2002; Merchant *et al*., 2002; Lurie *et al*., 2003)

Limitations of RFA are that the ablation catheters cannot be passed along tortuous superficial veins and the manufacturers suggest that treatment is limited to veins of <12mm diameter, meaning that up to 50% of patients are unsuitable for this technique. (Rautio *et al*., 2002) Also, RFA only replaces the ligation and stripping parts of SVS, and thus additional treatment, usually avulsions or UGFS, are required in the majority of patients to treat residual varicosities. (Merchant *et al*., 2005; Mundy *et al*., 2005)

1.3.3 Endovenous laser ablation

EVLA was first introduced in 1999 by Diomed (Cambridge, UK) and aims to ablate the GSV using a diode laser. EVLA is also performed using tumescent anaesthesia. As the laser is fired heat is generated in the blood around the tip and steam bubbles are produced and it is the action of these steam bubbles, and direct action of the laser on the vein wall, that causes the damage (collagen contraction and endothelial destruction) resulting in venous occlusion. (Proebstle *et al*., 2002)

Reported early occlusion rates are at least 90%, and persistent occlusion at up to two years is found in 90-100% in uncontrolled studies. (Navarro *et al*., 2001; Min *et al*., 2003; Proebstle *et al*., 2003b) The main complications are bruising and thrombophlebitis, although skin burns and paraesthesia also occur. DVT is rare after EVLA. Limitations are similar to those of RFA except treatment does not need to be limited to veins <12mm in diameter. As with RFA, EVLA only treats the GSV so additional treatment is often required (30-40%) for visible varicosities. There are many different laser systems on the market now with little evidence to guide clinicians as to which is best.

1.3.4 Sclerotherapy

Sclerotherapy has been in use for treating VV for over 150 years, but was popularised by Fegan in 1963. (Tisi and Beverley, 2004) However, high recurrence rates of over 50% in patients with SFJ or SPJ incompetence has lead to liquid sclerotherapy being reserved in the UK for the treatment of superficial varicosities without any identifiable saphenous reflux or for residual VV after SVS. (Hobbs, 1974;

Galland *et al*., 1998) The idea of using sclerosant in the form of a foam, rather than liquid, has been around for more than 70 years. Foam has been shown in a randomized controlled trial (RCT) to be significantly more effective than liquid in treating saphenous reflux, (Hamel-Desnos *et al*.,2003) and over the last few years UK vascular surgeons have begun to embrace UGFS, performed on an outpatient basis under local anaesthesia, as an alternative to SVS for truncal VV. In this Thesis I shall concentrate on this modality of treatment.

1.4 Ultrasound-guided foam sclerotherapy

1.4.1 Mechanism of action and choice of sclerosant

Sclerotherapy is the introduction of a substance into the lumen of a vessel with the intention of causing thrombosis and, subsequently, fibrosis. Sclerosing solutions produce endothelial damage that evolves to fibrosis, with the extent of damage to the blood vessel wall determining the effectiveness of the solution. Destruction of the endothelium exposes subendothelial collagen fibres initiating platelet aggregation and adherence and activating the intrinsic coagulation pathway. The inflammatory reaction at the vessel wall and the organization of the resultant thrombus result in fibrosis, causing obliteration of the vessel lumen. Excessive thrombosis causes discomfort and also can allow recanalisation of the vessel and compression bandaging is usually employed in an attempt to minimize this. (Sadick, 2000)

Sclerosants can be classified into three groups according to the mechanism by which they cause endothelial damage, with the ideal sclerosant being painless to inject and

free of any adverse effects. Detergent sclerosants include polidocanol, sodium tetradecyl sulphate (STS), and sodium morrhuate and they cause endothelial damage by altering the surface tension around the endothelial cell, allowing rapid overhydration (maceration). Osmotic agents, including hypertonic saline, produce damage by dehydration of the endothelial cell. The final category is the chemical irritants, such as chromate glycerine and polyiodinated iodide, which act as corrosives. (Sadick, 2000)

The most commonly used sclerosants in the treatment of VV are STS and polidocanol. STS is a long-chain fatty acid salt and is painless to inject, but can cause extravasation necrosis. It is usually used in concentrations of 1% to 3% to treat large VV and it produces maceration of the endothelium within one second of exposure. Polidocanol is a urethane anaesthetic agent which is also painless to inject and has a minimal risk of causing extravasation necrosis compared with other sclerosants. It is usually used in concentrations of 0.5% to 3%.

The use of foamed sclerosant has several important benefits over liquid sclerosant: it displaces blood preventing dilution and inactivation of the sclerosant, it has a much larger surface area incurring a greater sclerosing ability, it is possible to manipulate the foam once it has been injected to ‘steer’ the sclerosant in the correct direction, it has a greater volume and therefore fills more of the vein, and it is visible on DUS.

Sclerosing foam is a mixture of a physiologic gas and a detergent sclerosing solution, but within this definition foams can differ dramatically from one another. Physiologic gases are those which are either readily absorbed by the blood or can pass rapidly across pulmonary gas exchange membranes, including oxygen, carbon dioxide,

nitrous oxide and helium. A microfoam is one comprising bubbles which are smaller than 250 microns, allowing a larger surface area and better contact with the endothelium. Debate continues around the ideal technique for producing and administering the most effective foam.

1.4.2 History and development of foam preparation techniques

A comprehensive article reviewing the history of sclerosing foams has recently been published and is summarized here. (Wollman, 2004) McAusland first described the use of 'froth' that he prepared by shaking a bottle containing sodium morrhuate for the treatment of telangiectasia in 1939. Two modifications of the technique were described in 1944. The first by Orbach, who described the 'air block' technique, where a volume of air (no more than 3ml) was injected into the vein ahead of the sclerosant. The theory being that the air would displace the blood in the vein allowing increased contact of the sclerosant with the vein wall. It was later shown by Stemmer *et al.* in 1970 that the 'air block' technique was only reliable in veins of diameter up to 4mm. Also in 1944, Foote described the technique of mixing ethanolamine oleate with air to form an air/liquid dispersion for injecting telangiectasia. This so-called 'agitation technique' is no longer in use. In 1949 Sigg described a 'foam block' technique, where he injected foam instead of air, followed by liquid sclerosant. He found that foamed sclerosant was less rapidly washed away than air.

Orbach published a further paper in 1950 describing the use of a foam which he created by 'vigorously shaking' a syringe containing air and sclerosant to produce a froth and injected after an 'air block'. He found a four-fold increase in efficacy when

compared with liquid sclerosant. Ree was the first doctor in 1953 to describe the use of a pure foam technique without the use of an ‘air block’.

In 1956 Fluckiger discussed many important properties of foam and suggested another technique, the ‘aspiration technique’ in order to produce a fine-bubbled foam. This involved aspiration of the sclerosant and air simultaneously into a syringe through a narrow lumen injection needle. He also described the technique of ‘retrograde injection’ whereby the sclerosant is injected proximally into the saphenous vein with the leg held in an elevated position. Fluckiger went on in 1962 to describe another technique for foam preparation by pumping sclerosant and air backwards and forwards between the drug vial and a syringe, a technique that was later modernized by Frullini in 2000 by adding an adaptor between the bottle and the seal.

Mayer and Brucke described a double-plunger syringe specifically for the production of sclerosant foam in 1957. This device has an inner plunger with several tiny holes which is moved rapidly backwards and forwards to mix sclerosant and air within the syringe while the external plunger is held in a fixed position.

Gillesberger described a low-pressure technique in 1969, which was based on the creation of a negative pressure in a glass syringe. Monfreux later modified this in 1997, but a consistent problem with the two techniques is the inability to produce a standard ratio between air and sclerosant, thus producing foam with different qualities each time.

In 1986 Grigg introduced a new technique based on turbulent flow between two syringes connected by a plastic infusion tube, allowing the sclerosant and air to be

pumped back and forth. This technique was known as the ‘Irvine technique’ after the laboratory where the technique was demonstrated and is a precursor of Tessari’s technique and the double-syringe system.

Cabrera described his ‘rotating brush technique’ in 1995 where foam was agitated using a high-speed rotating brush. Another addition was the use of carbon dioxide rather than air as a carrier gas. He also suggested a high volume technique intending to completely fill the venous lumen with foam; this has been associated with high incidence of DVT and is no longer recommended.

In 1999 Mingo introduced the ‘foam medical system’ which generates foam by the introduction of gases from a cylinder and passes the mixture through a fine nozzle.

Currently Tessari’s ‘Tourbillon technique’, introduced in 2000, is the most commonly used technique of foam production and, as mentioned, is based on the ‘Irvine technique’ but with the use of a three-way tap instead of connection tubing. Sclerosant and air mixture is pumped forwards and backwards approximately 20 times. The liquid to air ratio varies from 1:3 to 1:4. By varying the size of the passage of the three-way tap it is possible to create higher turbulence and thus smaller, more stable, bubbles. Foam produced in this way is stable for approximately two minutes. A similar technique, the ‘double-syringe system’ was introduced in 2001 and instead of the three-way tap, uses an adaptor to connect the syringes and a 0.2-micron filter.

Clearly there are many ways of creating foam and therefore comparisons of efficacy from the literature are somewhat complicated. This is not helped by the many ways of administering the foam in use.

1.4.3 Variations in technique for administration

1.4.3.1 Cannulation and injection

Several different techniques of delivering the foam to the vein have been described and none to date has been proven to be better than the others.

Cabrera described direct cannulation of the saphenous trunk to be treated under DUS guidance. He then injected foam until it completed filled the vein along with its tributaries. Any tributaries that remained unfilled were injected using a butterfly needle. (Cabrera *et al*., 2000)

In France, the direct puncture technique is favoured, whereby the saphenous trunk is injected using a needle and syringe. (Hamel-Desnos *et al*., 2003) The entire length of the incompetent trunk and its tributaries is treated by several injections, often carried out over a number of sessions. While the direct puncture technique is simple to perform it can be risky, particularly in the popliteal fossa due to the proximity of several arteries to the SSV. Intra-arterial injection of sclerosant can result in extensive skin loss. (Biegeleisen *et al*., 1993; Bergan *et al*., 2001)

An alternative method is to indirectly fill the saphenous trunk via a major tributary often by placing a butterfly needle into the tributary. It is thought that indirectly filling the saphenous trunks in this manner will be less effective than direct injection as the foam is likely to mix with blood when filling the vein, producing more thrombosis rather than endothelial injury, making permanent sclerosis less likely.

In terms of volume of foam to be injected, a wide range of maximum suggested volumes have been reported. One group has used volumes of up to 40ml, (Cabrera

et al., 2004) whereas others used a maximum of 2.5ml. (Hamel-Desnos *et al*., 2003) A consensus document suggested that 6-8ml of foam per session is the maximum appropriate amount, (Breu and Guggenbichler, 2004) and this has since been increased to 12ml in 2006. (Breu *et al*., 2008)

1.4.3.2 Bandaging and compression

It is conventional to apply some form of compression following UGFS although there is little scientific evidence to support this practice. Examining the published literature, some groups have used stockings alone, (Tessari *et al*., 2001) others used a combination of bandages and stockings, often changed to stockings alone after a few days (Cabrera *et al*., 2000; Frullini and Cavezzi, 2002; Barrett *et al*., 2004; Yamaki *et al*., 2004) but Hamel-Desnos and colleagues used no stockings and no bandaging at all in their patients. (Hamel-Desnos *et al*., 2003) The usual duration of compression, when used, was two to three weeks.

1.4.4 Patient selection

Deep venous occlusion, severe peripheral arterial disease and extreme obesity are absolute contraindications to UGFS (they are also contraindications to SVS). Virtually all primary and recurrent VV are suitable, given sufficient operator expertise and experience, in contrast to the techniques requiring passage of a catheter (RFA and EVLT). Warfarin does not need to be stopped.

Other adverse patient factors to be considered are extreme frailty, severe comorbidity including cardiovascular, respiratory or malignant conditions, and those patients who are 'needle-phobic' or who request treatment under general anaesthesia. Very thin patients and those with very large varices may be left with palpable and visible lumps or skin pigmentation and are less suitable for treatment.

1.4.5 Evidence for efficacy and safety

The many different techniques of foam production and administration outlined above, along with the fact that many authors do not comment on their techniques, make interpretation of the available literature difficult.

Cabrera *et al.* published their findings in 2000 of the outcome of 500 GSV treated with a foam made from 1-3% polidocanol and carbon dioxide using an undisclosed technique, and administered by direct cannulation of the GSV in the thigh. At three years they found that 81% of GSV were obliterated and 96.5% of superficial branches were obliterated. This required one session of sclerotherapy in 86% of patients, two in 11% and three sessions in 3% of patients. They found no serious complications and no DVT in their series. (Cabrera *et al*., 2000)

In 2001, Tessari *et al*. presented their results of their pilot study using Tessari's technique to create the foam. Twenty-four patients with saphenous or recurrent varices were treated within a group of 77 patients, with 1-3% STS. A maximum of 8ml foam was used and one to four treatments were required. At one month they found that 'almost 100% were obliterated'. They reported two patients with transient scotomas and one case of thrombophlebitis. (Tessari *et al*., 2001)

Frullini and Cavezzi reported their results of a comparison of the Monfreux and Tessari techniques of generating foam from Italy in 2002. They treated 167 ‘medium or large’ veins with a mean of 1.8 sessions of up to 4ml of STS or polidocanol foam made using the Monfreux technique; and a further 170 ‘medium or large’ veins using a mean of 1.8 sessions injecting a mean of 2.7ml STS foam made using the Tessari technique. In the Monfreux group, immediate success was found in 88.1%, with five episodes of transient visual disturbance, one partially occlusive popliteal DVT and four episodes of skin necrosis. In the Tessari group they found immediate success in 93.3%, with one episode of visual disturbance, two partially occlusive popliteal DVT and two episodes of skin necrosis. (Frullini and Cavezzi, 2002)

In 2003, Hamel-Desnos *et al*. reported the outcome of an RCT comparing liquid and foamed 3% polidocanol. They created their foam using the double-syringe system and used direct puncture to treat GSV 4-8mm in diameter. In the foam group, 84% of the 45 patients had no residual reflux at three weeks; compared with 40% of the liquid group. They reported no episodes of skin necrosis in either group. At six months there were two recanalizations in the foam group, and six in the liquid group. (Hamel-Desnos *et al*., 2003)

Barrett *et al*. published their findings from New Zealand in 2004. They treated 99 saphenous veins (79 GSV) with a diameter of less than 10mm and 17 (14 GSV) with a diameter of more than 10mm. They used 3% STS foam, generated by Tessari’s technique with 1-2.5% polidocanol for branches. In the <10mm group, a mean of 2.2 treatments was required (follow-up treatments were only allowed up to three months). At two years, 92% of visible varicosities were successfully treated, 69% had complete sclerosis, and 97% had no reflux. In the >10mm group, a mean of 2.8 treatments

were required. At two years, 94% of visible varicosities were successfully treated, 77% had complete sclerosis, and 88% had no reflux. Of the whole group, 86% showed an improvement in their symptoms, and 100% felt their treatment had been successful. Phlebitis occurred in less than 5%, there were no major DVT or pulmonary embolism (PE), but there were six 'minor' DVT; five in a gastrocnemius vein and one in a posterior tibial vein. (Barrett *et al*., 2004)

Also in 2004, Yamaki *et al*. published their results from Japan. They treated 77 GSV with 1% and 3% polidocanol. Foam was used to treat 37 and liquid in the remaining 40 (not randomized). Foam was prepared using Tessari's technique and only one injection was given, although the volume injected is unclear. At 12 months they found vein occlusion in 68% of those treated with foam, compared with 18% of those treated with liquid. Recurrent VV were present in 8% of the foam group, and 25% of the liquid group. They do not comment on their complications of treatment. (Yamaki *et al*., 2004)

Cabrera *et al*. also reported on the outcome of 151 patients with CVU from Spain in 2004. They used their polidocanol and carbon dioxide microfoam created using a patented technique (Varisolve®, BTG International Ltd., London, UK). They treated either saphenous veins or incompetent perforators and used 20-30ml of foam to treat saphenous trunks, and 1-4ml to treat perforators. A mean of 3.6 treatments was required (range 1-17). They found complete ulcer healing in 86% of patients at six months, and a 6.3% recurrence rate at two years (70% of the original cohort was reviewed at two years). They reported no DVT, two episodes of transient visual disturbance, two episodes of dry cough lasting for less than one minute, and 10%

had thrombophlebitis. Skin pigmentation was seen in 20% but this had resolved in 90% of cases by six months. (Cabrera *et al*., 2004)

Since the commencement of our own studies towards the end of 2004, several other authors have published their findings on the efficacy and safety of UGFS. These are included in the Discussion sections of the various clinical chapters where appropriate.

1.5 Outcome assessment in venous disease

Traditional measures of outcome from surgical procedures including morbidity and mortality are less useful in the assessment of interventions for CVD, which is chronic and not life- or limb-threatening, as they give little information about the patient's experience of the disease. (McDaniel *et al*., 2000) Extended outcome assessment, including measures of technical success, clinical status, functional status, satisfaction and cost, enables us to achieve a more complete understanding of the effectiveness of different interventions, allows health-care providers and patients to make better decisions, and also allows us to deliver the most appropriate, cost-effective and medically-effective care. (McDaniel *et al*., 2000)

1.5.1 Technical success

Technical success following interventions for VV is usually measured by DUS. DUS is non-invasive, safe and reliable and is ideal for multiple assessments over time. Colour images of specific veins and the blood flow within them is provided by

combining real-time ultrasound imaging with pulsed Doppler information. When combined with the Doppler spectrum analysis, information about the patency of veins and the presence and duration of any reflux is gained.

Technical and anatomical success can be defined as occlusion of the treated saphenous trunk, determined by a lack of compressibility and the absence of any flow, or absence of the treated vein following SVS. Unfortunately, many published studies on outcome following minimally invasive treatment for VV use different definitions of technical success, thus making comparison difficult. The majority of these studies have also concentrated on primary GSVV; little has been published on either the treatment of recurrent VV after previous SVS or on the treatment of SSVV.

1.5.2 Clinical status

In the setting of CVD, measures of clinical status include those that quantify the outcomes that are meaningful to the patient. These include the safety of the procedure, relief of the presenting symptoms, healing of CVU and time to recurrence, and improvement in appearance.

1.5.2.1 Improvement in symptoms

A number of methods can be used to assess improvement in symptoms following intervention. Objective measures of certain symptoms (such as a pain scale) can be used over time to show improvement, patients can be asked to rate the improvement

in their symptoms, or a validated measure of symptom status (such as the disease-specific HRQL measures detailed below) can be used.

The most important thing when assessing improvement in symptoms is the pre-operative assessment and determining whether the patient's lower limb symptoms are likely to be due to their CVD. The symptoms that are often ascribed to CVD are fairly non-specific and are found in up to 50% of the adult population, (Bradbury *et al*., 1999) and the relationship between symptoms and objective evidence of CVD is weak. (Bradbury *et al*., 1999; Bradbury *et al*., 2000) Little work has been done examining the improvement in symptoms as an outcome of minimally invasive techniques; indeed only one group have looked at symptom improvement after UGFS. (Barrett *et al*., 2004)

1.5.2.2 Disappearance of VV and ulcer healing

No measures of determining improvement in appearance have been validated in patients with VV. It is important to differentiate between true VV (dilated, tortuous subcutaneous veins) and other types of visible superficial veins including reticular veins and telangiectasia. Reticular veins are dilated and tortuous subcutaneous veins that do not belong to the main saphenous trunk or its major tributaries. These veins are visible below the skin, sometimes even when normal. They typically become dilated in response to back pressure from truncal varices or an incompetent perforating vein, however, in certain patients no obvious source can be found, even on careful clinical and DUS examination. Telangiectasia, also known as hyphenweb or spider veins, are dilated intradermal venules that can occur in association with

trunk or reticular varices or in isolation. It is also important to differentiate between VV that are residual (still present after initial treatment) and those that are recurrent (initially disappeared after treatment, but now returned). The position of the VV must also be considered as those arising from reflux in a different saphenous trunk are representative of progression of disease, rather than recurrence.

CVU healing can be defined as complete re-epithelialisation of the leg, and ulcer recurrence as any loss of skin continuity below the knee. Studies have found that ulcer recurrence rates are significantly lower after SVS, but that ulcer healing was unaffected. (Barwell *et al*., 2004) The results of one study suggest that CVU healing may be accelerated after UGFS, but this relationship requires further examination. (Cabrera *et al*., 2004)

1.5.3 Functional status (Health-related quality of life)

HRQL is a multidimensional concept that incorporates general health, physical and psychological functioning, physical symptoms and the ability to interact socially. (Skevington and Tucker, 1999) Measuring HRQL is a comprehensive way to assess the effect of VV on patients, and whether interventions produce improvement. (Smith *et al*., 1999) Valuable information is gained on the patient-perceived burden of illness. HRQL is measured using structured questionnaires (also known as instruments) which have been developed in a scientifically rigorous manner adhering to specific psychometric properties. The questionnaire must be 'valid' and should measure what is intended; it must be 'reliable' and should give consistent results when repeated; it should be 'responsive' and should detect change in the condition of

interest; and it should be 'acceptable' by being easy to understand and complete. (McDaniel *et al*., 2000)

It is important when assessing HRQL to use both generic and disease-specific instruments. Generic instruments allow comparison of health status across groups by assessing the dimensions of HRQL that are common to all patients, but may be insensitive to some clinically important changes. Disease-specific instruments allow a more detailed and clinically relevant health assessment of the particular condition of interest. (McDaniel *et al*., 2000)

Both disease-specific and generic HRQL improve following SVS for VV, (Baker *et al*., 1995; Smith *et al*., 1999; Durkin *et al*., 2001; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam *et al*., 2004a) and more recently this has been shown to hold true for EVLA and RFA. (Rautio *et al*., 2002; Lurie *et al*., 2003) At the time of commencing the studies included in this Thesis the effects of UGFS on HRQL are unknown.

1.5.3.1 Generic health-related quality of life

The Short Form-36 (SF36) from the Medical Outcomes Survey is the most common generic HRQL measure used to demonstrate improvement after SVS. (Baker *et al*., 1995; Smith *et al*., 1999, Durkin *et al*., 2001; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam *et al*., 2004a) It consists of 36 questions assessing eight health status domains, and also provides two summary scores; the physical component summary score (PCS) which represents what a person can do, and the mental component summary score (MCS) which represents how a person feels. The SF36 has been widely used in many languages in many different clinical conditions and

'norms' have been created to allow comparisons with the general population. (Bowling *et al*, 1999) The mean PCS and MCS of the general population are 50 with a standard deviation of 10: the higher the score, the better the HRQL.

The Short Form-12 (SF12, **Appendix 1**) is a fully-validated adaptation of the SF36. It consists of 12 questions (developed from a subset of the original SF36 questions) also giving two summary scores, the PCS and MCS, and is faster and easier to complete and has been shown to give results comparable to those of the SF36. (Jenkinson *et al*., 1997; Hurst *et al*., 1998; Ware *et al*., 2002) The SF12 is scored using published regression weights and scoring rules, in particular, if any SF12 question is unanswered, the SF12 summary scores are recorded as missing. (Ware *et al*., 2002)

1.5.3.2 Venous disease-specific health-related quality of life

A variety of venous disease-specific HRQL measures have been developed and validated. The most commonly used is the Aberdeen Varicose Vein Symptom Severity Score (AVSS, **Appendix 2**). (Garratt *et al*., 1993; Garratt *et al*., 1996; Smith *et al*., 1999; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b) The AVSS comprises 13 questions about leg symptoms and signs, and a diagram where the patient can draw their VV. After weighting, it provides a final score between 0 and 100; a higher score denotes more symptoms and so a poorer disease-specific HRQL. Other validated measures include the VEINES-QOL/Sym and Chronic Venous Insufficiency Questionnaire (CIVIQ) questionnaires. (Launois *et al*., 1996; Lamping *et al*., 2003)

1.5.4 Satisfaction

Patient satisfaction is the least well standardized measure of extended outcome assessment. Satisfaction depends on addressing the main complaint of the patient and as such it is important to realize the patient's expectations prior to commencing treatment. Little has been published on the expectations of patients undergoing treatment for VV, but up to 20% of patients have expressed dissatisfaction with SVS. (Davies *et al*., 1995; Ray, 2005; Scurr and Scurr, 2005)

1.5.5 Cost

Methods of measuring cost depend on the perspective of measurement. From the patient's perspective, time lost from normal activities would be most important, but for the health-care provider the direct costs of providing treatment are most important. Cost calculations are frequently omitted from early attempts to measure extended outcomes because of their complexity. (McDaniel *et al*., 2000) Adverse outcomes from SVS can have a significant impact on the young and economically active population undergoing treatment for VV, and thus minimally invasive techniques which are associated with less morbidity and consequently a quicker return to normal activities and to work will be beneficial.

CHAPTER 2. THE EFFICACY OF ULTRASOUND-GUIDED FOAM SCLEROTHERAPY FOR CHRONIC VENOUS DISEASE

SVS is still considered by many to be the 'gold standard' treatment for VV. In order to be considered a useful treatment for VV, UGFS should therefore be at least as effective as SVS. Traditional objective measures of success of any intervention for VV include the technical (anatomical) success of the procedure, and the clinical success as judged by the disappearance of visible VV and, where appropriate, healing of CVU.

In this Chapter I assess the effectiveness of UGFS in terms of technical and clinical success in the treatment of both GSVV and SSVV. In addition I assess the effect of UGFS on healing of CVU.

2.1 Duplex ultrasound and clinical outcomes following ultrasound-guided foam sclerotherapy of symptomatic primary great saphenous varicose veins

The data contained within this Chapter were

- presented (poster) at the West Midlands Surgical Society in Birmingham, UK in November 2008
- presented (poster) at the International Surgical Congress of the Association of Surgeons of Great Britain and Ireland in Glasgow, UK in May 2009
- published in the European Journal of Vascular and Endovascular Surgery in October 2010 (Darvall *et al*., 2010a)

2.1.1 Introduction

SVS comprising ligation of the SFJ, stripping of the above-knee GSV (AK-GSV) and multiple stab avulsions remains the preferred treatment for symptomatic GSVV among UK vascular surgeons. Although such surgery improves lower limb symptoms, venous haemodynamics and HRQL, (Smith *et al*., 1999; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam *et al*., 2004a) it can be associated with a significant incidence of troubling and sometimes serious complications, morbidity, delayed return to work, as well as medico-legal activity. (Tennant and Ruckley, 1997; Corder *et al*., 1991; Sam *et al*., 2004a; Subramonia and Lees, 2005; Wood *et al*., 2005; Beale and Gough, 2005; Ray, 2005) Furthermore, previous studies of surgical

GSV stripping have reported a significant primary technical failure and recurrence rate. (MacKenzie *et al*., 2002b) Thus, despite best attempts to strip the GSV, post-operative DUS not infrequently reveals reflux in residual (remnant) GSV segments in the thigh. Furthermore, most surgeons are reluctant to strip the GSV below the knee for fear of causing saphenous nerve injury. Such residual disease in the AK- and BK-GSV is a well-recognised cause of clinically significant recurrent disease.

Minimally invasive techniques, such as UGFS, offer significant advantages over SVS although durability, and specifically late recanalisation, remains incompletely defined. The aim of this study, therefore, is to describe DUS and clinical outcomes 12 months following UGFS of symptomatic primary GSVV.

2.1.2 Methods

2.1.2.1 Patients

Following local ethical committee approval and after obtaining written informed consent, consecutive patients undergoing UGFS for symptomatic primary GSVV between November 2004 and May 2007 were invited to take part in the study. All patients were NHS patients referred to the Heart of England NHS Foundation Trust (HEFT) by their general practitioners. All patients were assessed in a consultant-led NHS outpatient clinic by one of two consultant surgeons (Professor AW Bradbury and Mr DJ Adam) prior to enrolment in the study.

To be considered suitable for inclusion patients had to have symptomatic venous disease (i.e. treatment was not offered for cosmetic indications), to have significant

reflux (>0.5s) in the GSV confirmed on DUS, and to be willing to undergo UGFS. Patients who had had previous SVS for GSVV on the same leg were excluded from the study. Patients with absent pedal pulses or an ankle-brachial pressure index (ABPI) of <0.8 were excluded, as were those with post-thrombotic deep venous occlusion.

2.1.2.2 Pre-treatment assessment

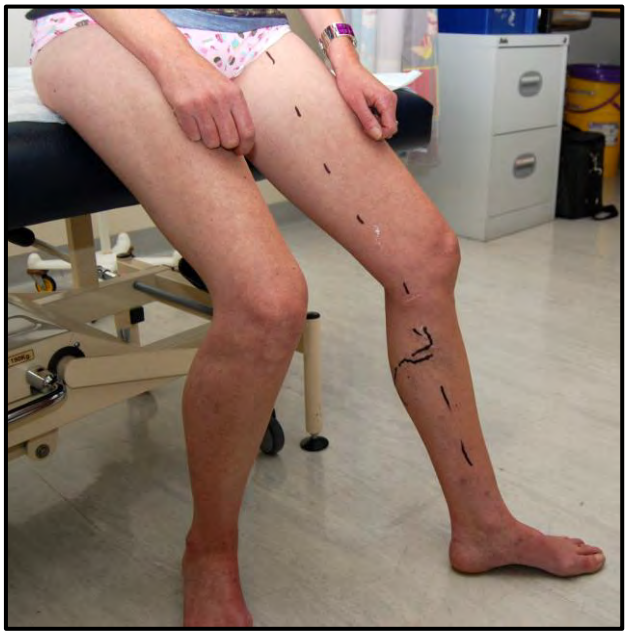
Patients were examined and the severity of venous disease according to the CEAP clinical classification was determined (**Table 1.1**). (Eklof *et al*, 2004) All patients had either visible varicosities (C_2 or C_3) or skin complications (C_4, C_5 or C_6).

All patients underwent DUS at their initial outpatient clinic appointment to identify sites of SVR and DVR. All DUS examinations were performed in a standard manner. Patients were examined standing with their weight on the contralateral limb and the leg to be examined slightly bent with the heel on the floor to relax the calf muscle while maintaining stability, with a Sonosite Micromaxx® (Sonosite Ltd, Hitchin, Herts, UK) fitted with a 10-MHz transducer. The following venous segments were insonated: proximal and distal superficial femoral vein; above- and below-knee popliteal vein; SFJ and SPJ; the whole length of the GSV, SSV and anterior accessory saphenous vein (AASV). All veins were assessed for patency and compressibility. Reflux was induced with a manual calf squeeze and was considered pathological when it exceeded 0.5 seconds.

2.1.2.3 UGFS treatment

All UGFS treatments were performed on an outpatient basis in a treatment room, and took less than 30 minutes. Patients with bilateral VV had only one leg treated at a time (usually worst leg first); the second leg was treated at least four weeks later. Immediately before treatment the incompetent truncal veins and superficial varices were marked on the skin using DUS (**Figure 2.1**).

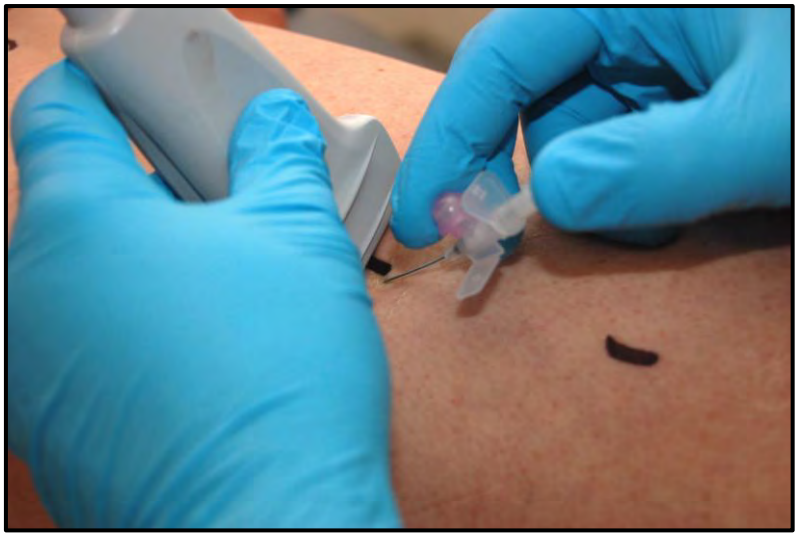
Figure 2.1 Pre-treatment skin marking



The patient then reclined in the supine position for cannulation of the GSV. Peripheral intravenous catheters (Optiva^{TM}; Medex Medical, Rossendale, UK) were inserted under direct ultrasonographic guidance (**Figure 2.2**). According to the size and depth of the target vein, 18-22G cannulae (green, pink or blue) were used. Once

all cannulae were secured, the leg was elevated (to empty the veins) for injection of the foam (**Figure 2.3**). All cannulae were flushed with normal saline to ensure that they were not dislodged during the changes in leg position.

Figure 2.2 Ultrasound-guided cannulation of the GSV



Sclerosant foam was prepared by Tessari's method using two 2ml syringes connected by a three-way tap and a 5 micron filter (B Braun Medical, Sheffield, UK), and comprised 0.5ml of 3% STS (Fibrovein®; STD Pharmaceuticals, Hereford, UK) and 2ml of air (**Figure 2.4**). Foam was injected in 2ml aliquots, and its distribution and resultant venous spasm observed by DUS. At least 30 seconds was left between injecting each aliquot of foam. After each injection patients were asked to dorsi- and plantar-flex their ankle several times to clear any foam that might have entered the deep venous system.

Figure 2.3 Elevation of the leg prior to foam injection

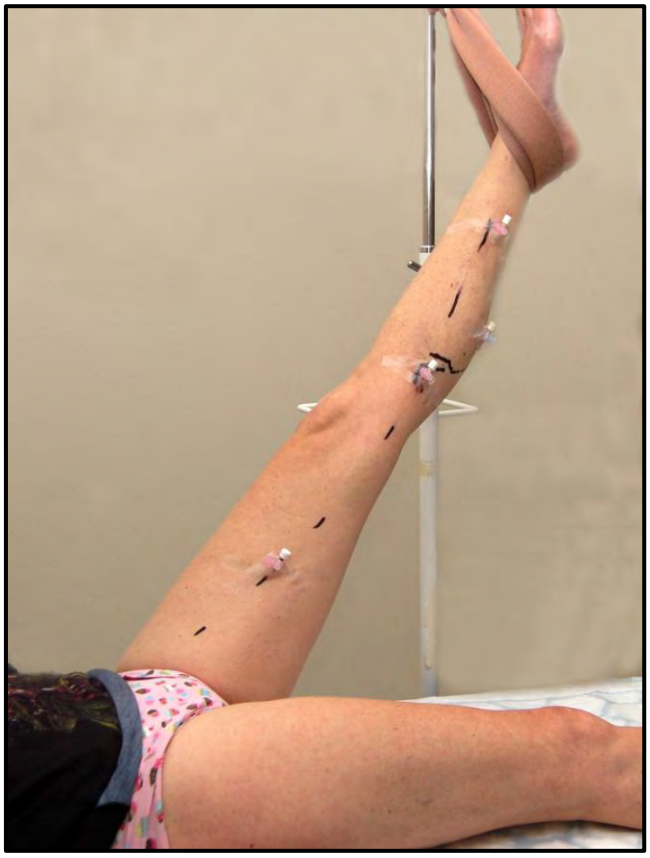
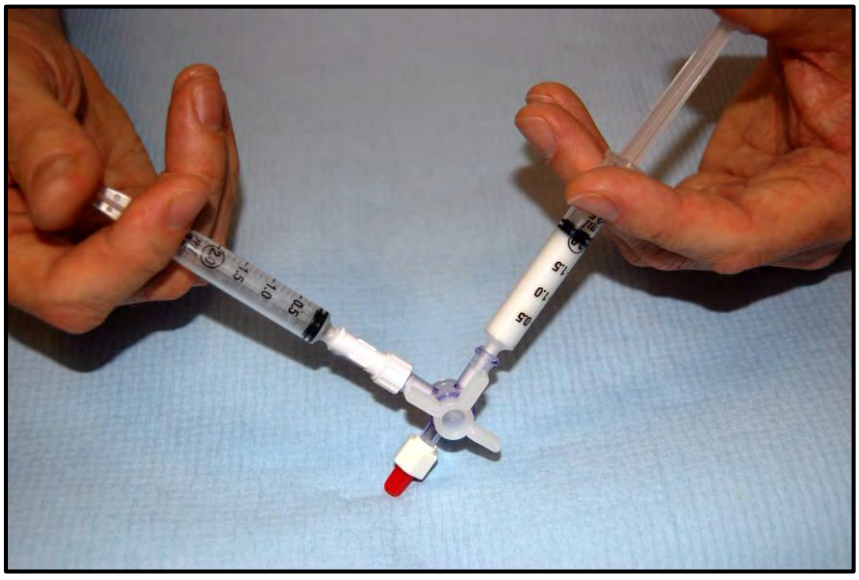


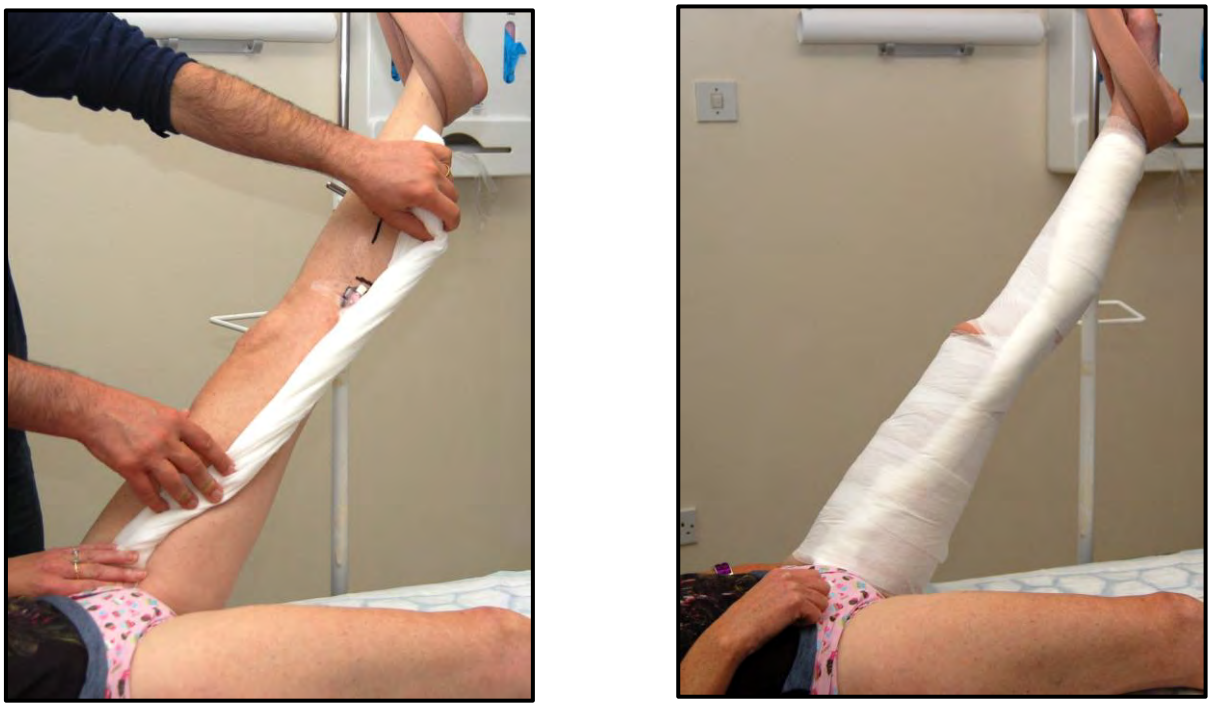
Figure 2.4 Tessari's method of foam preparation



When all the trunk and tributary veins and the varices were in spasm, and filled with foam, the cannulae were removed and compression was applied with the leg still elevated.

A roll of Velband® (Johnson and Johnson Medical, Ascot, UK) was applied directly along the line of the previously marked saphenous trunk and superficial varices (**Figure 2.5**), and retained using Pehahaft® cohesive bandage (Hartmann, Heidenheim, Germany) (**Figure 2.5**). The bandage was then secured with Medipore® (3M Company, USA) 100mm wide adhesive tape. This regimen produced direct compression over the treated truncal veins.

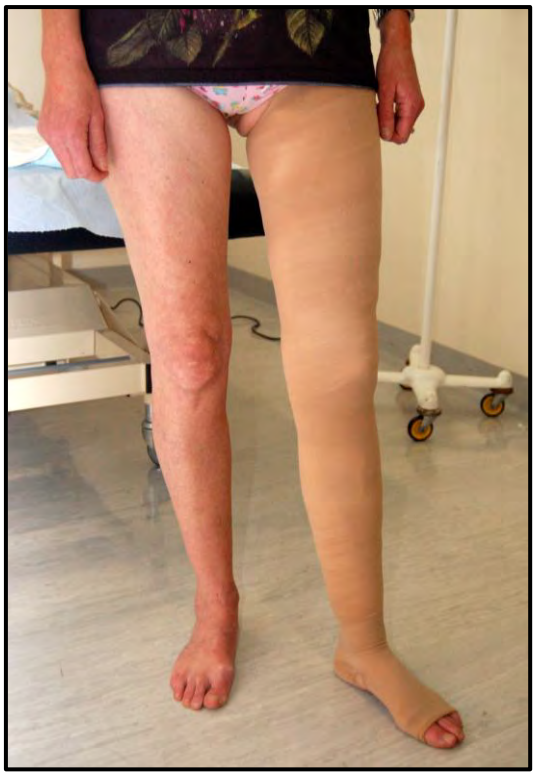
Figure 2.5 Post-treatment bandaging



A thigh-length European (RAL) class II compression stocking (Credelast®; Credenhill, Ilkeston, UK) was applied over the bandage (**Figure 2.6**). The bandaging was left intact for five to ten days, depending on the size of the veins, after which it was removed and the class II stocking worn alone for a further three weeks.

After the procedure patients were required to walk for around 10 minutes and then it was suggested that they walk for at least five minutes during every waking hour while the bandages were *in situ*. Patients were told to take analgesia as required, to return to driving when they felt able to perform an emergency stop and to return to work when they felt comfortable. Patients were given a contact telephone number to use if they experienced severe discomfort or had any other concerns following treatment.

Figure 2.6 Thigh-length compression stocking applied over bandage



Patients with residual or recurrent VV at any follow-up appointment were offered further treatment, either by direct injection of 1% polidocanol liquid (Sclerovein®, Resinag AG, Zurich, Switzerland) or 0.5% or 1% STS foam into the varicosities, or if saphenous truncal reflux was present by repeating UGFS with 3% STS (Fibrovein®) as outlined above.

2.1.2.4 Outcome measures and follow-up

The chosen outcome measures were complete occlusion of, and abolition of reflux in, the GSV on DUS (defined as technical success), and the complete absence of any visible VV (defined as clinical success). All patients were seen at one, six and 12 months after treatment in a dedicated research clinic. At the first visit the patients were also asked whether they had had any complications following their treatment. Patients were specifically asked about visual disturbance, headache, and possible nerve problems in the treated leg.

Repeat DUS was performed at each follow-up visit as per the pre-treatment DUS (described in **Section 2.1.2.2**). In addition, occlusion of the treated saphenous trunk was assessed by a lack of compressibility and the absence of any flow. Complete occlusion was defined as occlusion over the entire length of the GSV to the SFJ. Recanalisation was defined as the presence of flow in either an antegrade or retrograde direction in a previously occluded AK or below-knee (BK) GSV. Recanalisation was considered complete if over 50% of the length of vein had recanalised. Where recanalisation was found, the presence or absence of recurrent reflux was determined.

Patients with residual reflux or recanalisation at any follow-up appointment were offered further treatment by repeating foam sclerotherapy with 3% STS as outlined above.

At each follow-up appointment treated limbs were also examined to determine the presence of any visible trunk VV. The presence of reticular veins only was not recorded as clinical failure of treatment. The distribution (GSV, AASV, or SSV) of any residual or recurrent VV was recorded.

2.1.3 Results

2.1.3.1 Patients and treatments

The characteristics of the 278 patients (344 legs) undergoing UGFS for primary GSVV are shown in **Table 2.1**.

One, two, three and four cannulae were used in 123, 202, 18, and one treatments respectively. The median volume of 3% STS foam used at each treatment was 10 (range 2-16) ml.

Three patients complained of visual disturbance shortly after their injections which consisted of blurring of vision and in all cases lasted for less than 10 minutes. There was no DVT observed in this group of patients either clinically or on follow-up DUS. There were no reported cases of PE. There were no other complications.

Table 2.1 Patient and disease characteristics

Parameter	
No. of patients	278
No. of legs	344
Age: median (range) in years	57 (21-89)
Sex	
Male	103 (37.1)
Female	175 (62.9)
CEAP clinical grade	
C_2	213 (61.9)
C_3	24 (7.0)
C_4	72 (20.9)
C_5	14 (4.1)
C_6	21 (6.1)
A(E)tiology	
Primary (E_p)	344 (100)
Secondary (E_s)	0 (0)
Anatomical patterns of venous reflux	
Superficial and deep (A_{sd})	10 (2.9)
Superficial only (A_s)	334 (97.1)
Primary GSV above and below-knee	297 (86.3)
Primary GSV above-knee only	36 (10.5)
Primary GSV below-knee only	11 (3.2)
Pathophysiological classification	
Reflux (P_r)	344 (100)
Obstruction (P_o)	0 (0)

Figures in parentheses are percentages unless otherwise specified

2.1.3.2 Treatment of the AK-GSV

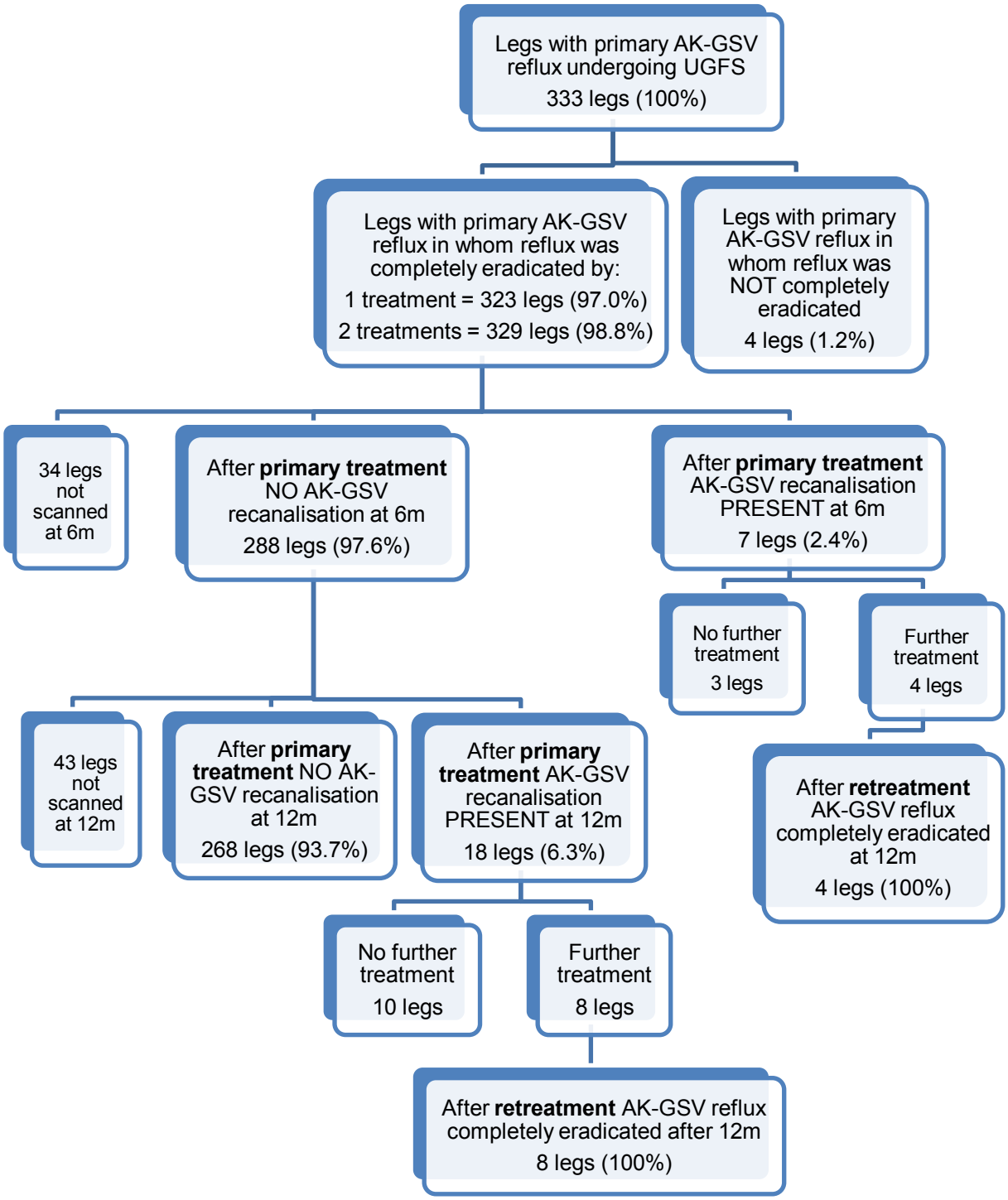
Complete eradication of reflux in the AK-GSV was achieved in 323/333 (97.0%) legs after one, and in a further 6/333 (1.8%) legs after two treatment sessions (course of primary treatment) (**Figure 2.7**). In four legs (1.2%) complete eradication of reflux in the AK-GSV was not achieved by one treatment session but these patients, despite residual reflux in the AK-GSV, were content with the clinical result and declined further treatment sessions.

In the 329 legs in whom the primary course of UGFS achieved complete eradication of the reflux in the AK-GSV, recanalisation was observed in 7/295 (2.4%) legs at 6 months and 18/286 (6.3%) legs at 12 months (**Figure 2.7**). 34 legs were not seen at 6 months; 43 at 12 months.

At 6 months this AK-GSV recanalisation was partial (<50%) without reflux in one leg and partial with reflux in six legs. Of these seven legs, four underwent one session of repeat UGFS which resulted in successful complete eradication of AK-GSV reflux, and three patients were content with the clinical result and declined further treatment.

At 12 months this AK-GSV recanalisation was partial without reflux in two legs, partial with reflux in 13 legs, and complete (>50%) with reflux in three legs. Of these 18 legs, eight underwent one session of repeat UGFS which resulted in successful complete eradication of AK-GSV reflux, and ten were content with the clinical result and declined further treatment.

Figure 2.7 Eradication of reflux and recanalisation in the AK-GSV after UGFS for primary GSVV



2.1.3.3 Treatment of the BK-GSV

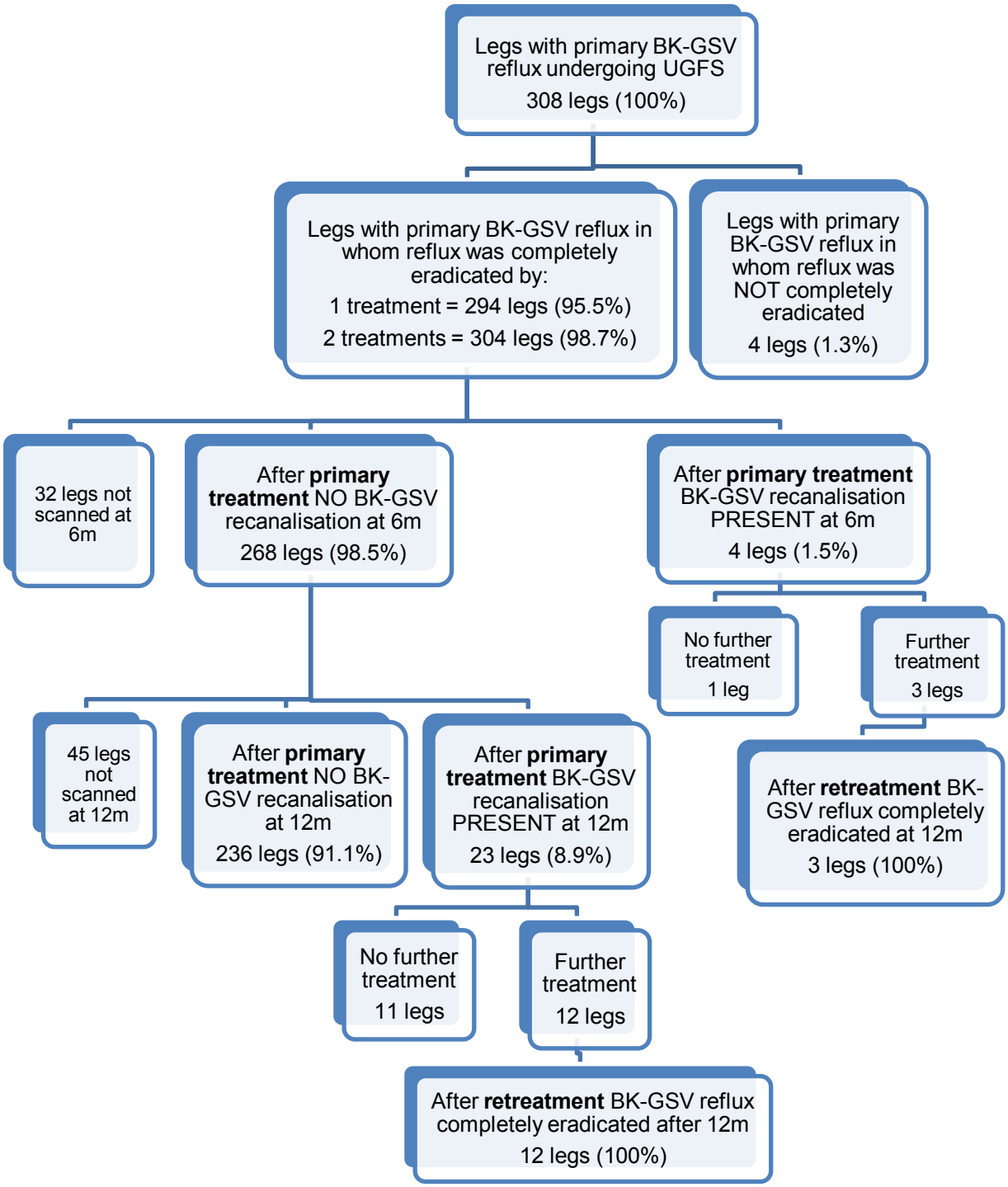
Complete eradication of reflux in the BK-GSV was achieved in 294/308 (95.5%) legs after one, and in a further 10/308 (3.2%) legs after two treatment sessions (course of primary treatment) (**Figure 2.8**). In four legs (1.3%), complete eradication of reflux in the BK-GSV was not achieved by one treatment session but these patients, despite residual reflux in the BK-GSV, were content with the clinical result and declined further treatment sessions.

In the 304 legs in whom the primary course of UGFS achieved complete eradication of the reflux in the BK-GSV, recanalisation was observed in 4/272 (1.5%) legs at 6 months and 23/259 (8.9%) legs at 12 months (**Figure 2.8**). 32 legs were not seen at 6 months; 45 at 12 months.

At 6 months this BK-GSV recanalisation was complete with reflux in all four legs. Of these four legs, three underwent one session of repeat UGFS which resulted in successful complete eradication of BK-GSV reflux, and one patient was content with the clinical result and declined further treatment.

At 12 months this BK-GSV recanalisation was partial without reflux in one leg, partial with reflux in seven legs, and complete with reflux in 15 legs. Of these 23 legs, 12 underwent one session of repeat UGFS which resulted in successful complete eradication of BK-GSV reflux, and for the remaining 11 legs the patient was content with the clinical result and declined further treatment.

Figure 2.8 Eradication of reflux and recanalisation in the BK-GSV after UGFS for primary GSVV



2.1.3.4 Clinical success

There were no visible VV in 304 legs (88.4%) after one treatment, and in 316 legs (91.9%) after two treatment sessions (course of primary treatment) to eradicate GSV reflux. Six legs had residual GSV reflux in association with residual VV after one session, but the patients were happy with the results and did not want further treatment. In 22 legs, there were still some residual visible VV after successful eradication of GSV reflux with just one session of treatment. For six of these legs, no further treatment was requested by the patient; and a single session of foam injections directly into the visible varicosities successfully treated the residual VV in the remaining 16 legs, giving a total of 332 legs (96.5%) with no visible VV after a maximum of two treatment sessions.

By 12 months, 273/311 (87.8%) still had no visible VV after their primary course of treatment (33 were lost to follow-up or had residual untreated VV). Six legs had recurrent VV in association with recanalisation at 6 months, and 19 had recurrent VV in association with recanalisation at 12 months. Fifteen of these 25 had further successful UGFS treatment resulting in both eradication of the reflux and disappearance of their recurrent VV; the remainder were happy with the clinical results. Ten legs had a few recurrent VV at 12 months but no recanalisation or reflux and only two of these wanted further treatment; three had VV secondary to new reflux in the SSV.

2.1.4 Discussion

The main findings of this study are that a single session of UGFS eradicates reflux in the AK- and BK-GSV in over 95% of patients with symptomatic primary GSV; recanalisation at 12 months is low (9% in the BK-GSV; 6% in the AK-GSV) and, when it does occur and leads to clinically significant varices, is easily treated with further UGFS.

Although still the preferred treatment among UK vascular surgeons, (Winterborn and Corbett, 2008) it is widely recognised that residual and recurrent GSV reflux are common after SVS for primary GSVV. MacKenzie *et al.* reviewed 66 patients two years after SFJ ligation and attempted GSV stripping in the thigh and found that 62% had AK and 69% had BK truncal reflux on DUS. (MacKenzie *et al*., 2002b) An RCT reported by Dwerryhouse *et al*. found that failure to strip the GSV was associated with an unacceptably high rate of recurrence. (Dwerryhouse *et al*., 1999). Van Rij and colleagues prospectively followed up 92 patients (127 limbs) after GSV surgery. (van Rij *et al*., 2003) and found that two weeks after SVS 1/100 SFJ ligations had clearly failed, with DUS demonstrating an intact SFJ. Clinical recurrence (defined as recurrent VV) in all limbs was progressive, present in 13.7% (17/124) at three months, 31.6% (36/114) at one year, and 51.7% (60/116) limbs after three years. Of 100 SFJ that were adequately ligated, 23 demonstrated recurrent reflux at three years, with most of the recurrences present by one year.

Although the primary aim of the current work is not to compare UGFS with the other currently available minimally invasive techniques, nevertheless, it is important and useful to place the current findings in context. During the study period and over the last few years there have been a number of RCTs comparing EVLA and, less

commonly, RFA with SVS; several meta-analyses and systematic reviews have been published.

Van den Bos *et al.* published a meta-analysis comparing SVS, RFA, EVLA and UGFS. (van den Bos *et al*., 2009) They included 72 studies, 13 SVS, 19 RFA, 30 EVLA and 10 UGFS. Only 9 were RCTs, 49 were prospective clinical series and the remaining 14 were retrospective case series. They only included studies that used DUS as the outcome measure with a total of 12320 limbs and an average follow-up of 32.2 months. Anatomic success rates of SVS were 80.4% at three months, reducing to 75.7% at five years; for RFA they were 88.8% at three months and 79.9% at five years; for EVLA they were 92.9% at three months and 95.4% at five years; and for UGFS they were 82.1% at three months reducing to 73.5% at five years. After adjusting for duration of follow-up they found that compared with SVS, UGFS and RFA were as effective, and EVLA significantly more effective. (van den Bos *et al*., 2009)

Both EVLA and RFA are also considered to be as effective as SVS for the treatment of primary GSV incompetence in terms of early recanalisation rates, and mid-term recurrence of visible VV. Following EVLA recanalisation rates of 0-9% at 1-2 years have been reported, (Min *et al*., 2003; Mundy *et al*., 2005; Theivacumar *et al*., 2009b, Christenson *et al*., 2010; Pronk *et al*., 2010) although one RCT comparing EVLA and RFA found recanalisation rates of 22% (7/32) and 26% (9/34) respectively 6 months after treatment. (Goode *et al*., 2010) Other studies found recanalisation in 0-19% of patients treated with RFA at 1 year. (Merchant *et al*., 2002; Merchant *et al*., 2005; Nicolini *et al*., 2005)

Recurrent visible VV have been reported in 6-26% of EVLA-treated limbs, (Theivacumar *et al*., 2009b; Disselhoff *et al*., 2009; Rasmussen *et al*., 2010; Pronk *et al*., 2010) and in 0-21% of RFA-treated limbs at 1-2 year follow-up. (Merchant *et al*., 2002; Merchant *et al*., 2005; Nicolini *et al*., 2005; Luebke and Brunkwall, 2008) In the RCTs comparing EVLA with SVS, there were no significant differences found in technical and clinical outcomes between the two groups. (Theivacumar *et al*., 2009b; Rasmussen *et al*., 2010; Christenson *et al*., 2010; Pronk *et al*., 2010)

Since commencing the studies included in this Thesis, several other groups have published their outcomes from UGFS. However, the majority of the available data regarding UGFS still comes from clinical series rather than RCTs. Two systematic reviews found occlusion rates of 84% and 87% (Luebke and Brunkwall, 2008; Jia *et al*., 2007) and recurrence of visible VV in 11% and 14% (Luebke and Brunkwall, 2008; Jia *et al*., 2007). The results from this study are superior to those published for UGFS and comparable with those reported with EVLA and RFA.

The effectiveness of SVS for GSV incompetence is also limited by the reluctance to strip the BK-GSV based on fear of damaging the saphenous nerve. (Sam *et al*., 2004b) Dwerryhouse *et al*. found that even in the legs that had undergone stripping to knee level, a quarter had incompetence in the residual BK-GSV at five years. They questioned the importance of this however, as many had no visible VV. (Dwerryhouse *et al*., 1999) Van Neer *et al*. prospectively followed 74 limbs that had undergone SFJ ligation and GSV strip to knee level for primary GSV incompetence. They reported BK-GSV reflux in 81% before SVS, 84% at six months, and 91% at two years, with visible VV in the BK-GSV in 16% at six months and 22% at two years, although they did not perform any stab avulsions which may explain the higher

incidence compared with other studies. (van Neer *et al*., 2009) They also found that there was a tendency to worsening of the clinical signs and symptoms between six months and two years after SVS.

Persistent reflux in the BK-GSV may lead to venous hypertension and thus to the signs and symptoms of CVD as evidenced by a smaller improvement in AVSS post-treatment in patients with residual BK-GSV reflux after EVLA. (Theivacumar *et al*., 2009a) In limbs undergoing AK-GSV EVLA without concomitant treatment to the BK-GSV, Theivacumar *et al*. reported that significant BK-GSV reflux was present in 15/23 (52%) at six weeks. (Theivacumar *et al*., 2009b) In their RCT they found that BK-GSV reflux was abolished in 23/23 (100%) limbs that underwent EVLA from mid-calf to groin (BK-EVLA) and that this was associated with significantly less additional sclerotherapy requirements (17% vs. 61%). Improvement in AVSS, pain scores and satisfaction were comparable in both groups, and importantly BK-EVLA was not associated with saphenous nerve injury. However, the authors comment that only 70% (67/95) limbs with primary BK-GSV reflux were suitable for BK-EVLA from mid-calf to groin because of BK-GSV tortuosity. (Theivacumar *et al*., 2009b)

By contrast, as is clearly demonstrated here, patients can be offered a primary course of UGFS treatment until all AK- and BK-GSV reflux has been eradicated. In most cases this requires only one treatment session using a modest volume of foam and is associated with a very low incidence of side-effects and complications. Furthermore, if recurrent reflux develops as a result of recanalisation it can be very simply and effectively treated, usually by a further single injection of foam.

One problem with UGFS is that the technique itself remains far from standardised and many variations on the basic theme exist. Despite seven years elapsing since commencing this study, there remains little consensus regarding techniques for foam preparation and delivery, and post-treatment compression making comparison and generalisation of the results achieved difficult. (Myers and Roberts, 2009; Cavezzi and Tessari, 2009; Coleridge Smith, 2009) There is further evidence from RCTs and a systematic review that UGFS is more effective in both the short and long-term than liquid sclerotherapy, (Wright *et al*., 2006b; Rabe *et al*., 2008; Ouvry *et al*., 2008; Hamel-Desnos and Allaert, 2009) and that 3% polidocanol foam is no more effective than 1%. (Hamel-Desnos *et al*., 2007; Blaise *et al*., 2010)

There have been two recent RCTs looking at bandaging and compression after UGFS. One group compared bandaging for 24 hours with bandaging for five days, both followed by a thromboembolus deterrent (TED) stocking for the remainder of two weeks. (O'Hare *et al*., 2010) They found no advantage in prolonged wearing of the compression bandages in terms of incidence of phlebitis, skin discolouration and post-procedural pain, improvement in HRQL and 6-week target vein occlusion rates. (O'Hare *et al*., 2010) The other study compared the use of compression stockings (15-20mmHg) worn during the day for three weeks with no compression at all. (Hamel-Desnos *et al*., 2010) They found no difference in occlusion of treated veins, side-effects (thrombophlebitis, inflammation, pain and pigmentation), satisfaction scores and HRQL improvement between the two groups.

It is clear that further controlled studies are required to determine optimum technique. We have honed our technique over the last ten years and it continues to develop and we think improve. For example, present data on eradication of GSV reflux appear

materially superior to those reported in a multicentre prospective trial of Varisolve® 1% polidocanol microfoam. (Wright *et al*., 2006b) EVLA and RFA technology is also evolving to improve the balance between desired and undesired effects. (Enzler and van den Bos, 2010)

In conclusion, the present study adds further evidence that UGFS is a safe and clinically effective treatment for primary GSVV. A primary course of UGFS comprising one and infrequently two treatment sessions, leads to complete eradication of GSV reflux in virtually 100% of cases. Recanalisation at 12 months in this study is superior to that reported after SVS and similar to that observed following other minimally invasive techniques.

2.2 Duplex ultrasound and clinical outcomes following ultrasound-guided foam sclerotherapy of symptomatic recurrent great saphenous varicose veins

The data contained within this Chapter were

- presented at the Venous Forum Spring Meeting at the Royal Society of Medicine, London, UK in April 2011
- published in the European Journal of Vascular and Endovascular Surgery in July 2011 (Darvall *et al*., 2011)

2.2.1 Introduction

Residual and/or recurrent GSV reflux is disappointingly common after SVS. For many years, authors have reported that around 20% of patients undergoing SVS for GSVV have been operated previously for GSVV in the same leg. (Bradbury *et al*., 1993; Negus, 1993) In our current UGFS practice we find that figure to be 21% suggesting that there has been little improvement in surgical outcomes in recent times.

Recurrence after GSVV surgery may be due to

1. Residual VV often because of failure to adequately strip a refluxing AK or BK-GSV at the first operation, (MacKenzie *et al*., 2002b)
2. True recurrence, often referred to as neovascularisation. (Jones *et al*., 1996) This can occur at the previously dissected SFJ or stripping track, or

3. Progression of disease, for example the development of new reflux in the AASV in the thigh.

All three pathologies often co-exist in the same patient and can be difficult to distinguish.

Redo GSVV surgery typically comprises re-exploration of the SFJ, stripping of the AK-GSV and multiple phlebectomies. Such surgery can be technically demanding and associated with a higher incidence of significant complications and re-recurrence than first time GSVV surgery. (Gibbs *et al*., 1999; Hayden and Holdsworth, 2001) Furthermore, reflux in the BK-GSV is similarly difficult to treat with further SVS.

Although the role of EVLA, RFA and UGFS in treating primary GSVV is becoming established, their effectiveness in the treatment of recurrent GSVV is less well defined. (Navarro *et al*., 2001; Merchant *et al*., 2002; Rautio *et al*., 2002; Weiss and Weiss, 2002; Lurie *et al*., 2003; Min *et al*., 2003; Proebstle *et al*., 2003b; Beale and Gough, 2005)

The aim of the present study, therefore, is to describe DUS and clinical outcomes 12 months following UGFS of symptomatic recurrent GSVV.

2.2.2 Methods

2.2.2.1 Patients

Following local ethical committee approval and after obtaining written informed consent, consecutive patients undergoing UGFS for symptomatic recurrent GSVV

between November 2004 and May 2007 were invited to take part in the study (as per **Section 2.1.2.1**).

Recurrence was defined as previous SVS to the GSV in the same leg on at least one previous occasion. Specifically, all patients had undergone attempted SFJ ligation and multiple phlebectomies, with or without attempted stripping of the GSV; in most cases this was to the level of the knee only.

To be considered suitable for UGFS patients had to have symptomatic, CEAP C_{2-6} venous disease (i.e. treatment was not offered for cosmetic indications) and significant (> 0.5seconds) reflux in a segment of residual above and/or below knee GSV on DUS. Patients with absent pedal pulses or an ankle brachial pressure index < 0.8 were excluded as were those with post-thrombotic deep venous occlusion.

2.2.2.2 Pre-treatment assessment

Patients were examined and the severity of venous disease according to the CEAP clinical classification was determined (**Table 1.1**).

DUS was performed, as described in **Section 2.1.2.2**, at the initial clinic attendance in order to identify sites of superficial, deep and communicating venous reflux.

2.2.2.3 UGFS treatment

UGFS treatment was performed as described in **Section 2.1.2.3**.

2.2.2.4 Outcome measures and follow-up

The chosen outcome measures were complete occlusion of, and abolition of reflux in, the GSV on DUS (defined as technical success) and the complete absence of any visible VV (defined as clinical success).

Patients were followed up at 1, 6 and 12 months as described in **Section 2.1.2.4** with DUS and clinical examination.

2.2.3 Results

2.2.3.1 Patients and treatments

The characteristics of the 73 patients (91 legs) undergoing UGFS for recurrent GSVV are shown in **Table 2.2**. In 88 legs there was reflux in the AK-GSV, of which 77 also exhibited reflux in the BK-GSV; isolated BK-GSV reflux was observed in only 3 legs.

Despite a previous SFJ dissection as evidenced by a previous scar, in 27 legs there was an apparently intact and incompetent SFJ refluxing into an incompetent residual AK-GSV. In 34 legs the SFJ appeared to have been (at least partially) ligated and there was collateral reflux into an incompetent residual AK-GSV through tributaries and/or neovascularisation. In the remaining 30 legs the SFJ had been satisfactorily ligated and the proximal (usually 5-10cm) AK-GSV removed but there was reflux in the AK and/or BK-GSV trunk below this point as a result of perforator incompetence. One, two, and three cannulae were used to introduce the foam in 36, 43, and 12 treatments respectively. The median volume of 3% STS foam used at each treatment was 8 (range 4-14) ml.

Table 2.2 Patient and disease characteristics

Parameter	
No. of patients	73
No. of legs	91
Age: median (range) in years	58 (32-86)
Sex	
Male	24 (33)
Female	49 (67)
CEAP clinical grade	
C_2	54 (59)
C_3	4 (4.5)
C_4	21 (23)
C_5	8 (9)
C_6	4 (4.5)
A(E)tiology	
Primary (E_P)	91 (100)
Secondary (E_S)	0 (0)
Anatomical patterns of venous reflux	
Superficial and deep (A_{SD})	5 (5.5)
Superficial only (A_S)	86 (94.5)
Recurrent GSV above and below-knee	77 (84.5)
Recurrent GSV above-knee only	11 (12)
Recurrent GSV below-knee only	3 (3.5)
Pathophysiological classification	
Reflux (P_R)	91 (100)
Obstruction (P_O)	0 (0)

Figures in parentheses are percentages unless otherwise specified

There was no clinical or DUS evidence of DVT or PE, no visual disturbance, nor any other complications or side effects.

2.2.3.2 Treatment of the AK-GSV

Complete eradication of AK-GSV reflux was achieved in all 88 legs; 86 (98%) legs after one treatment and in a further two legs after a second (course of primary treatment) (**Figure 2.9**).

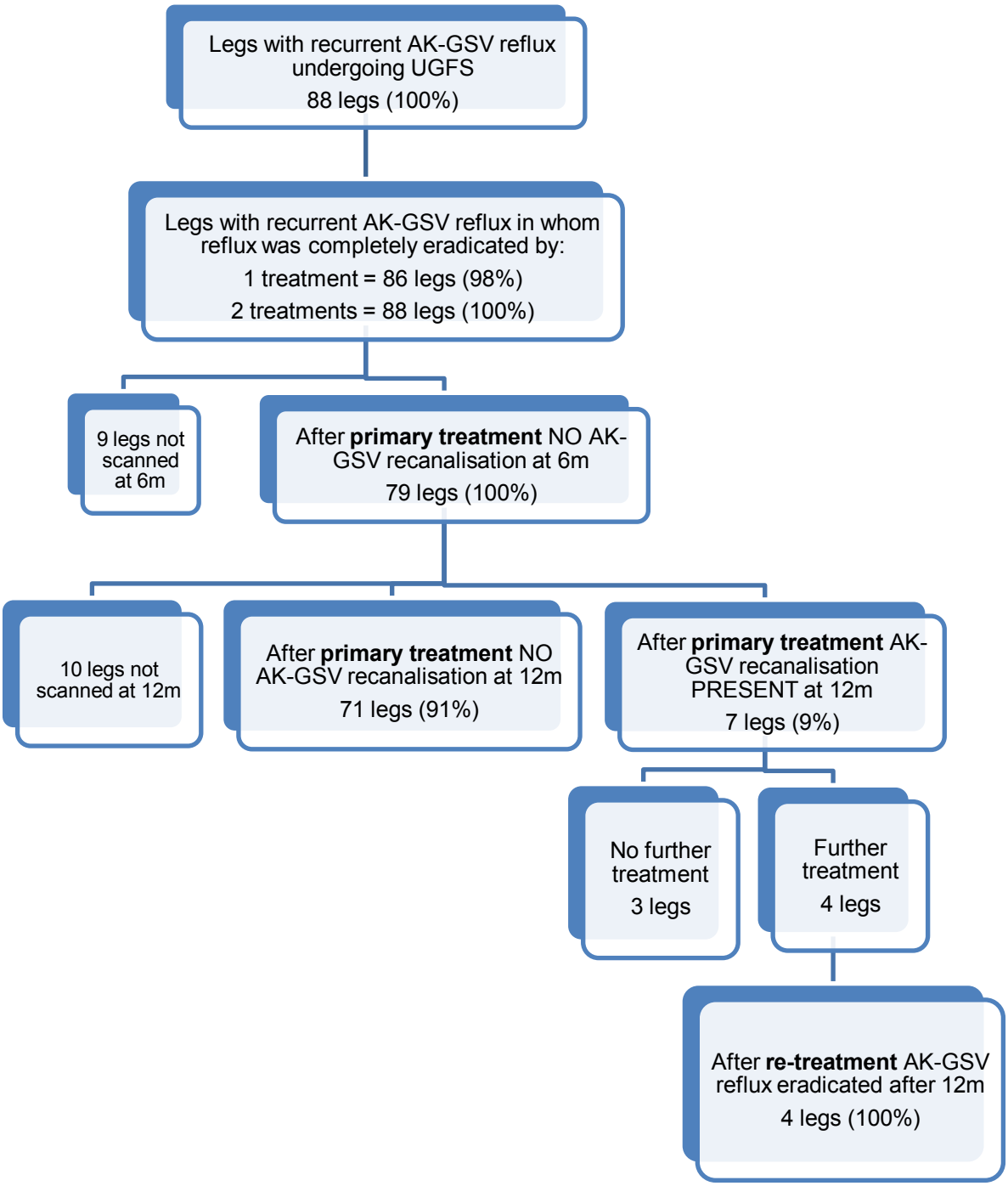
Recanalisation was observed in 0/79 (0%) scanned legs at 6 months and 7/78 (9%) scanned legs at 12 months (**Figure 2.9**). Nine and ten legs were not scanned at 6 and 12 months respectively because the patients defaulted from follow-up.

At 12 months this AK-GSV recanalisation was partial (<50% length) with reflux in four legs, and complete (>50%) with reflux in three legs. Of these seven legs, four underwent one session of repeat UGFS which resulted in successful complete eradication of AK-GSV reflux, and three were content with the clinical result and declined further treatment.

2.2.3.3 Treatment of the BK-GSV

Complete eradication of reflux in the BK-GSV was achieved in 77 (96.5%) legs; 74 (93%) legs after one, and in a further three (3.5%) legs after a second, treatment session (course of primary treatment) (**Figure 2.10**).

Figure 2.9 Eradication of reflux and recanalisation in the AK-GSV after UGFS for recurrent GSVV



In three legs (3.5%), complete eradication of reflux in the BK-GSV was not achieved after a single treatment session but these patients, despite residual reflux in the BK-GSV, were content with the clinical result and declined further treatment sessions.

In the 77 legs in whom the primary course of UGFS achieved complete eradication of the reflux in the BK-GSV, recanalisation was observed in 1/69 (1.5%) scanned legs at 6 months and 8/68 (12%) scanned legs at 12 months (**Figure 2.10**). Eight and 12 legs were not scanned at 6 and12 months respectively.

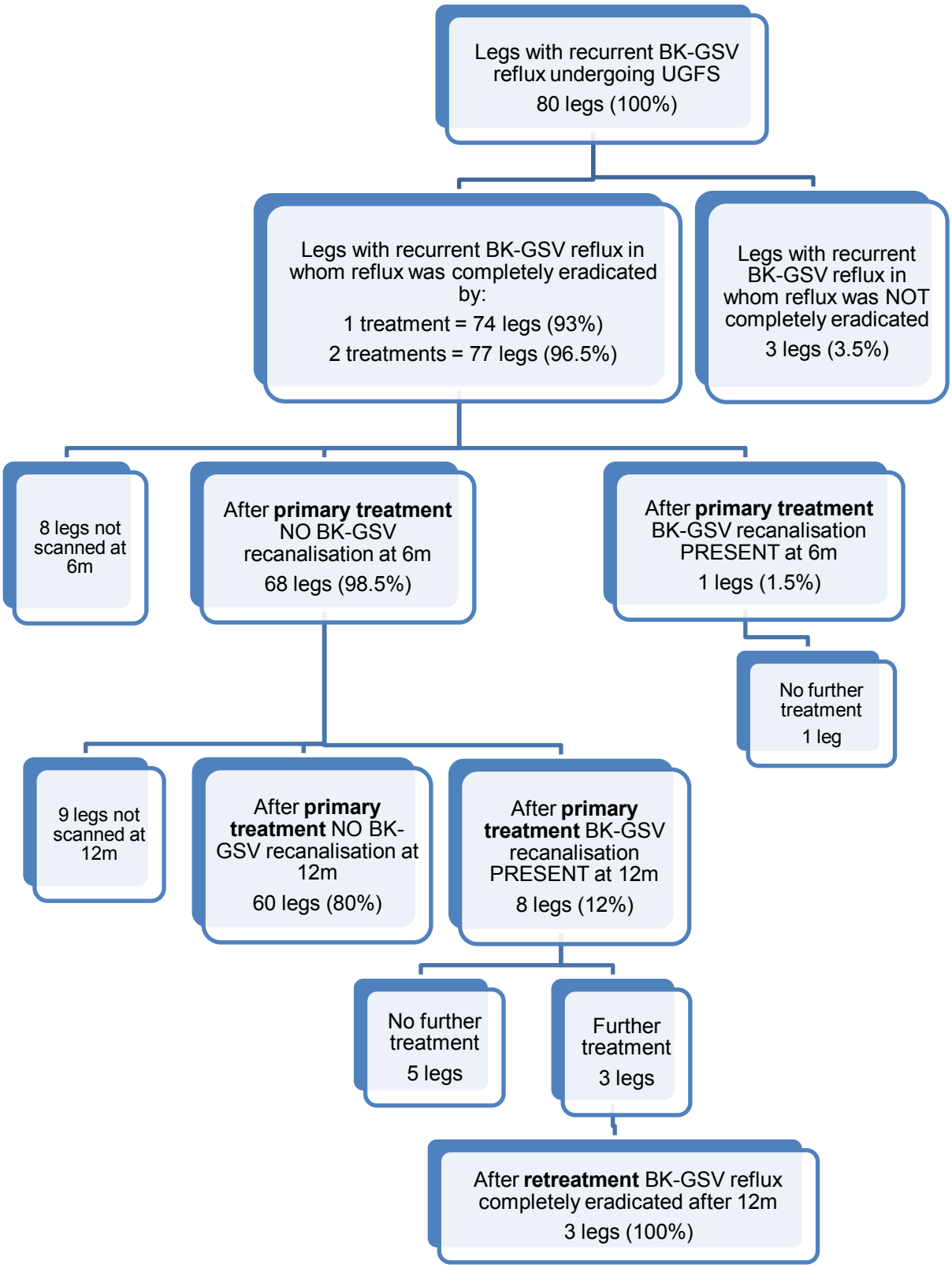
At 6 months this BK-GSV recanalisation was complete (> 50%) with reflux in the single leg, but the patient was content with the clinical result and declined further treatment.

At 12 months this BK-GSV recanalisation was partial (<50%) with reflux in three legs, and complete with reflux in five legs. Of these eight legs, three underwent one session of repeat UGFS which resulted in successful complete eradication of BK-GSV reflux, and for the remaining five legs the patient was content with the clinical result and declined further treatment.

2.2.3.4 Clinical success

There were no visible VV in 78 legs (86%) after one treatment, and in 83 legs (91%) after two treatment sessions (course of primary treatment) to eradicate GSV reflux. Two patients had a few residual VV in association with residual reflux after one treatment but were happy with their results and declined further treatment.

Figure 2.10 Eradication of reflux and recanalisation in the BK-GSV after UGFS for recurrent GSVV



In six legs, there were still some residual visible VV after successful eradication of GSV reflux with two treatment sessions. A single session of foam injections directly into the visible varicosities successfully treated the VV in all six legs.

By 12 months, 68/78 (87%) still had no visible VV after their primary course of treatment (11 were lost to follow-up; 2 had residual untreated VV). One leg had recurrent VV in association with recanalisation at 6 months (but declined further treatment), and seven legs had recurrent VV in association with recanalisation at 12 months. Four of these seven had further successful UGFS treatment resulting in both eradication of the reflux and disappearance of their recurrent VV; the remainder were happy with the clinical result. Three legs had a few recurrent VV at 12 months but no recanalisation or reflux, and none wanted further treatment.

2.2.4 Discussion

Many observers have reported disappointing results with redo SVS for residual and recurrent GSVV; and most surgeons would probably prefer not to do such surgery if an effective alternative could be found. (Gibbs *et al*., 1999; Hayden and Holdsworth, 2001)

Intuitively, therefore, it is in the treatment of recurrent VV that one might imagine that the new endovenous techniques would have their greatest appeal to patients and surgeons alike. But, somewhat surprisingly, data on the effectiveness of EVLA, RFA and UGFS for recurrent GSVV are relatively limited when compared to primary disease. (Rautio *et al*., 2002; Lurie *et al*., 2003; Beale and Gough, 2005; Hinchcliffe *et*

al., 2006; Pannier and Rabe, 2006; Rasmussen *et al*., 2007; Vasquez *et al*., 2007; Darwood *et al*., 2008)

Fassiadis *et al.* reported on the use of RFA in 18 legs with recurrent GSV. (Fassiadis *et al*., 2002) Fifteen legs had neovascularization connecting with a residual GSV, two had an incompetent thigh perforator, and one had a refluxing anterior thigh branch reconnecting with the GSV. They found occlusion of all 18 GSV at one month; and in 16/16 followed up to 12 months. One-third had temporary sensory disturbances. All returned to daily activities within three days.

Hinchcliffe *et al.* randomized 16 patients with bilateral recurrent GSVV to have one leg treated with RFA and the other with SVS comprising a lateral approach to the SFJ and GSV strip to the knee. (Hinchcliffe *et al*., 2006) All limbs had previously been treated with SFJ ligation and had an incompetent SFJ and reflux in the GSV on DUS. Prior to randomization they found that 70% of patients had a persistent and incompetent GSV suitable for treatment with RFA. GSV were considered unsuitable if excessively tortuous, or <3 or >12mm in diameter. The patients were followed up to 12 months and they found complete occlusion in 13/16 GSV treated with RFA, and complete GSV stripping in 14/16 legs treated with SVS. RFA was significantly quicker to perform and associated with less pain and bruising.

van Groenendael *et al.* retrospectively compared outcomes in 149 patients that underwent SVS and 67 patients that underwent EVLA for recurrent GSVV. (van Groenendael *et al*., 2009) All limbs had a recurrent SFJ and had reflux in a part of the GSV. In the surgically-treated group 87% had had previous GSV stripping, and in the EVLA group 57% had had stripping. All had had previous SFJ disconnection. All

treatments were deemed successful immediately after treatment and in the 46% (69%) legs scanned 8 weeks after EVLA, all treated veins remained occluded. At a median follow-up of 13.5 months 26% of SVS patients had 'clinical recurrence' (although a definition for this is not given in the paper and repeat DUS was not performed), compared with 12% in the EVLA group at a median follow-up of 15 months. However, after adjusting for length of follow-up this difference was not statistically significant. They also found less post-treatment pain in the SVS group, but more analgesia usage. Wound infection occurred in 8% of the SVS group. They conclude that 'if anatomically suitable' EVLA is a good treatment alternative for recurrent GSVV, however, they also point out that only 31% of patients with recurrent GSVV were suitable for EVLA. Various reasons were given for unsuitability: 37% tortuosity of the GSV, 8% GSV diameter <4mm, 4% presence of thrombophlebitis, 51% other reasons including veins too branched or superficial and too many connections with the deep venous system. This finding was confirmed recently in a study that found that only 44/113 (38.9%) of legs with recurrent GSV reflux were suitable for treatment with EVLA or RFA. (Goode *et al*., 2009)

Four groups have looked at UGFS for recurrent GSVV. Kakkos *et al.* presented immediate results of 45 legs with recurrent GSVV treated with UGFS (3% STS foam). (Kakkos *et al*., 2006) Twenty-eight had groin reflux, five perforator vein, and the remainder had isolated GSV remnant reflux. A single injection of 6ml was adequate in 58% of legs; 11% needed three or more treatment sessions. However, complete elimination of reflux at the end of treatment was only achieved in 39/45 (87%) legs. Follow-up was only for three weeks.

Darke *et al.* treated 18 legs with recurrent GSVV with UGFS (3% polidocanol foam). (Darke and Baker, 2006) All had persistent or reconstituted GSV trunks in continuity with superficial varicosities and usually with the femoral vein in the groin. Legs were assessed clinically and with DUS after six weeks. Ten legs had complete occlusion after one treatment; a further five had complete occlusion after two treatments. The three remaining legs had partial occlusion (either GSV still open but varicosities all closed, or less than complete GSV occlusion but patient satisfied) after one, two or three treatments.

Coleridge Smith reported his experience with using UGFS (mostly 3% STS foam) for 267 recurrent GSVV in 2006. (Coleridge Smith, 2006) Further information about the type of recurrence was not given. One hundred and six legs (40%) were reviewed at least six months (mean 11 months) following treatment. The GSV was occluded in 98/106 (92.5%); better than the 86% occlusion rate seen in primary GSV.

O'Hare *et al.* reviewed 32 legs six months after UGFS (3% STS foam) for recurrent VV. (O'Hare *et al*., 2008a) They found occlusion of treated veins on DUS at six months in 23/32 (72%), and 28/32 (88%) were satisfied with the results of treatment. Unfortunately, this represented less than 50% of their treated cohort and they gave no further information regarding the type of recurrence treated. They also included some patients treated for SSV rather than GSV recurrence.

In conclusion, the present study adds further evidence that UGFS is a safe and clinically effective treatment for recurrent GSVV. A primary course of UGFS, comprising one and infrequently two treatment sessions, leads to complete eradication of GSV reflux in virtually 100% of cases. Recanalisation at 12 months is

superior to that reported after SVS and similar to that observed following other minimally invasive techniques. Recanalisation is easily and successfully treated with a further single UGFS treatment.

2.3 Duplex ultrasound and clinical outcomes following ultrasound-guided foam sclerotherapy of symptomatic small saphenous varicose veins

The data contained within this Chapter were

- presented (poster) at the West Midlands Surgical Society in Birmingham, UK in May 2009
- published in the British Journal of Surgery in November 2009 (Darvall *et al*., 2009).

2.3.1 Introduction

Approximately 20% of patients presenting with VV have SSVV. (Engelhorn *et al*., 2005) The literature indicates that the surgical approach to SSVV remains contentious, (Winterborn *et al*., 2004) and that the outcomes are often suboptimal. The SSV and SPJ are subject to considerable anatomical variation, and surgery is often difficult, ineffective and associated with complications, including paraesthesia, and high recurrence rates. (Tong *et al*., 1996; Rashid *et al*., 2002; van Rij *et al*., 2003, Sam *et al*., 2004b) Most studies examining the safety and efficacy of minimally invasive alternatives to SVS have focused on GSVV, and their role in the treatment of SSVV remains incompletely defined. EVLA and RFA are currently used to treat SSVV with high success rates, but they are not suitable for all patients, often require additional stab avulsion or UGFS, and can be associated with complications such as paraesthesia. (Proebstle *et al*., 2003a; Merchant *et al*., 2005)

The aim of the present study, therefore, is to describe DUS and clinical outcomes 12 months following UGFS for symptomatic SSVV.

2.3.2 Methods

2.3.2.1 Patients

Following local ethical committee approval and obtaining written informed consent, consecutive patients undergoing UGFS for symptomatic SSVV between November 2004 and May 2007 were invited to take part in the study (as per **Section 2.1.2.1**).

To be considered suitable for UGFS patients had to have symptomatic, CEAP C_{2-6} venous disease (i.e. treatment was not offered for cosmetic indications) and significant (>0.5 seconds) reflux in the SSV on DUS. Patients with absent pedal pulses or an ABPI <0.8 were excluded, as were those with post-thrombotic deep venous occlusion.

2.3.2.2 Pre-treatment assessment

Patients were examined and the severity of venous disease according to the CEAP clinical classification was determined (**Table 1.1**).

DUS was performed, as described in **Section 2.1.2.2**, at the initial clinic attendance in order to identify sites of superficial, deep and communicating venous reflux.

During the study period all patients presenting to the study team with SSVV were offered UGFS and SVS, and all chose UGFS.

2.3.2.3 UGFS treatment

UGFS treatment was performed as described in **Section 2.1.2.3**, except the SSV was cannulated with the patient reclining in the prone position rather than supine.

2.3.2.4 Outcome measures and follow-up

The chosen outcome measures were complete occlusion of, and abolition of reflux in, the SSV on DUS (defined as technical success) and the complete absence of any visible VV (defined as clinical success).

Patients were followed-up at one, six and 12 months as described in **Section 2.1.2.4** with DUS and clinical examination. Complete occlusion in the SSV was defined as occlusion over the entire length of the treated SSV up to the first meeting with a deep vein, usually the popliteal vein, but sometimes a gastrocnemius vein.

2.3.3 Results

2.3.3.1 Patients and treatments

Table 2.3 summarizes the baseline characteristics for each of the 92 legs (86 patients); 60 legs had UGFS for isolated SSVV and the remaining 32 also underwent UGFS for co-existing GSVV at the same treatment session. In the 60 legs undergoing treatment for SSVV alone, a single cannula was used in 58 legs, and two cannulae in the other two. The median volume of foam used was 6 (range 2-8) ml.

Table 2.3 Patient and disease characteristics

Parameter	
No. of patients	86
No. of legs	92
Age: median (IQR) in years	57 (47-66)
Sex	
Male	28 (33)
Female	58 (67)
CEAP clinical grade	
C_2	62 (67)
C_3	10 (11)
C_4	14 (15)
C_5	6 (6)
C_6	0 (0)
A(E)tiology	
Primary (E_p)	92 (100)
Secondary (E_s)	0 (0)
Anatomical patterns of venous reflux	
Deep (A_d)	0 (0)
Superficial only (A_s)	92 (100)
Primary SSV alone	47 (51)
Recurrent SSV alone	13 (14)
Primary SSV and primary GSV	22 (24)
Primary SSV and recurrent GSV	9 (10)
Recurrent SSV and primary GSV	1 (1)
Pathophysiological classification	
Reflux (P_r)	92 (100)
Obstruction (P_o)	0 (0)

Figures in parentheses are percentages unless otherwise specified

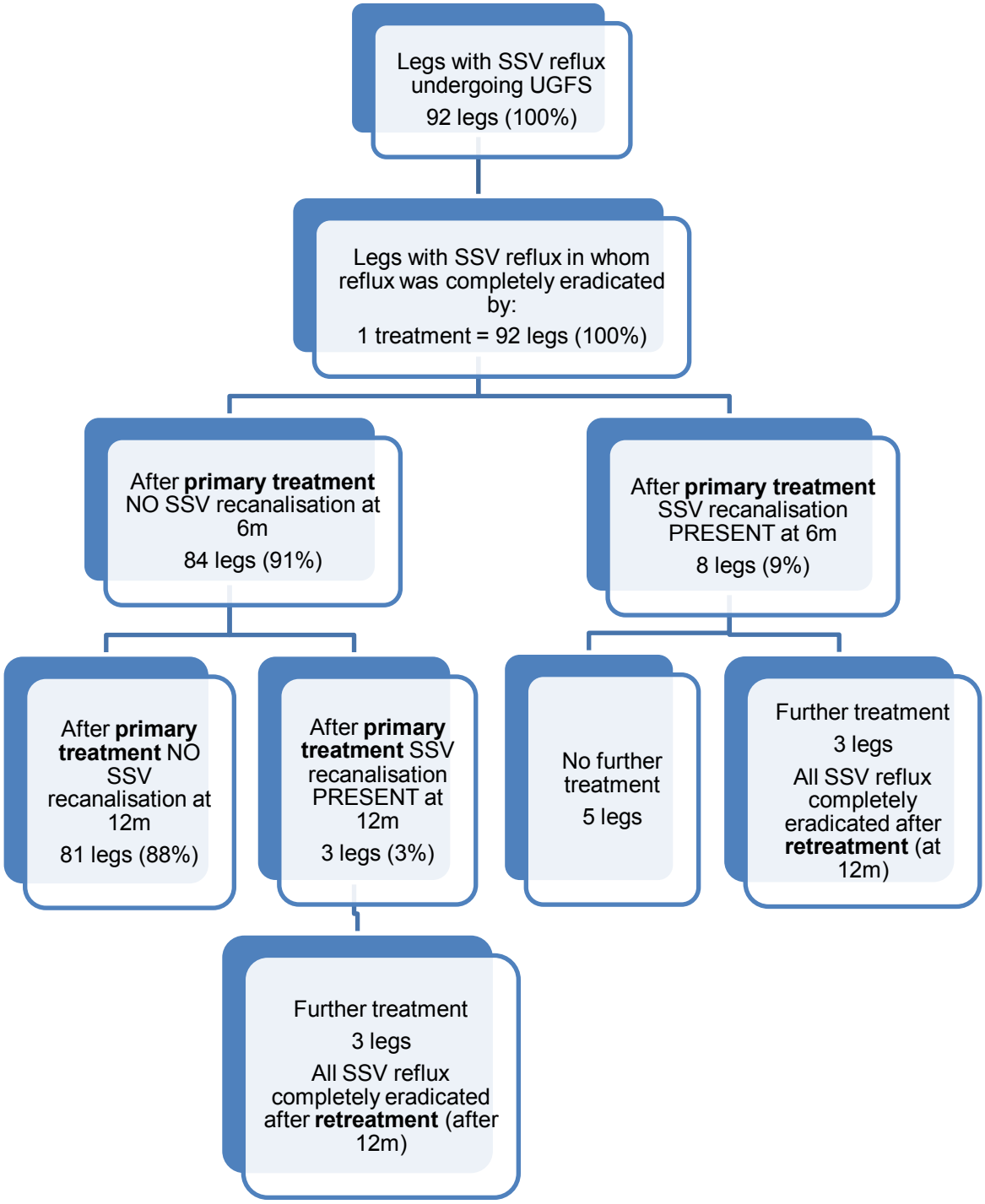
In the 32 legs undergoing simultaneous treatment for GSV incompetence a median of 2 (range 2-4) cannulae were used, with a median volume of 10 (range 6-16) ml of foam.

There was one symptomatic popliteal vein thrombosis that was detected four days after treatment and remained localized to the area of the SPJ. After six months of treatment with warfarin this patient was found to have mild (new) popliteal vein incompetence; the SSV remained occluded, there were no visible VV and the patient was asymptomatic. There were no other complications or adverse side-effects and, in particular, no visual/neurological symptoms nor symptoms of nerve injury in the treated leg.

2.3.3.2 Technical success

At one and six months, the technical success rates (complete SSV occlusion without reflux) were 100% and 91% (84/92 legs) respectively (**Figure 2.11**). At six months, seven patients had SSV that had partially recanalised and exhibited reflux, and one patient had reflux at the SPJ into a tributary while the SSV remained occluded. Of these eight technical failures, six had some associated visible VV (clinical failure) but only three patients wanted further treatment (the others were happy with the outcome) and in all cases this was technically and clinically successful. Thus including the three patients who had a second treatment the technical success rate at 12 months was 91% (84/92). None of the 14 patients undergoing UGFS for recurrent SSVV following previous SVS experienced a technical failure out to 12 months.

Figure 2.11 Eradication of reflux and recanalisation in the SSV after UGFS



2.3.3.3 Clinical success

At one month, four legs (4%) had some visible VV present. The SSV was occluded without reflux in all of these patients. Two patients wanted and underwent tidy-up injections of these tributaries and reticular veins at this stage.

At six months, nine legs (10%) had some visible VV and in six cases this was due to recanalisation of the main SSV or a tributary. In the remaining three legs, the VV were due to new GSV incompetence. Six of these legs underwent further UGFS at between six and twelve months. At 12 months, six legs (7%) had visible VV (clinical success rate 93%). Three were associated with SSV recanalisation that was present at six months; there were two further SSV recanalisations, and one patient had VV in association with an incompetent below-knee perforating vein.

2.3.3.4 Missing data

All 86 patients attended one-month follow-up. Three patients did not attend follow-up at six months, but when seen at one and 12 months they had complete technical and clinical success and so have been assumed to have had successful treatment at six months. Two patients did not attend follow-up at 12 months, but when seen at six months and subsequently at two years they had complete technical and clinical success, so are assumed to have had treatment success at 12 months. A further two patients did not attend 12-month follow-up, but when seen at six months they had recanalisation of the SSV and recurrent visible VV for which they did not want any additional treatment. These were included in the 12-month analysis as treatment failures so as not to underestimate the recurrence rate at 12 months.

2.3.4 Discussion

The main finding of this study in terms of treatment of the SSV, is that UGFS is a safe, technically (91%) and clinically (93%) effective treatment for SSVV out to 12 months. In 89/92 limbs a single treatment was sufficient. The only complication in the current study was a short, occlusive popliteal vein DVT that resolved following six months of warfarin. This patient had no identifiable risk factors for DVT and the reason for the thrombosis in this particular patient remains unclear. In particular there were no cases of transient visual disturbance or other central neurology or features of nerve injury in the treated leg.

By contrast, the literature indicates that the surgical approach to SSVV remains challenging and that outcomes are often disappointing in terms of recurrence and a high incidence of significant complications. (Tong *et al*., 1996; Rashid *et al*., 2002; van Rij *et al*., 2003, Sam *et al*., 2004b; Winterborn *et al*., 2004; Allegra *et al*., 2007; O'Donnell and Iafrati, 2007; Winterborn and Corbett, 2008; O'Hare *et al*., 2008b) Popliteal fossa anatomy is highly variable and potentially treacherous. Despite pre-operative duplex marking, SVS is often technically inadequate with an intact SPJ being reported in 24-47% patients at six weeks (**Table 2.4**). (Rashid *et al*., 2002; van Rij *et al*., 2003; O'Hare *et al*., 2008b; Ikponmwosa *et al*., 2010) In one recent prospective multicentre observational study paraesthesia was present in 27% of limbs at six weeks, and in the majority this persisted to 12 months. (O'Hare *et al*., 2008b) Two studies reported visible recurrent VV in 26% and 30% of patients at one and five years respectively. (Allegra *et al*., 2007; O'Hare *et al*., 2008b)

Table 2.4 Published outcomes from SVS, EVLA, RFA and UGFS of the SSV

Name and year	n	Follow-up	No reflux	No visible VV	DVT	Paraesthesia
SVS						
Rashid *et al*., 2002	59	6wk	31/59 (53)	-	2/59 (3)	-
Van Rij *et al*., 2003	33	2wk	25/33 (76)	-	-	-
		5y	12/33 (36)	-	-	-
Allegra *et al*., 2007	132	5y	-	93/132 (70)	-	-
O'Hare *et al*., 2008b	234	6wk	123/230 (53)	201/226 (89)	0	62/230 (27)
		1y	82/203 (40)	151/204 (74)	-	46/204 (23)
Ikponmwosa *et al*., 2010	90	6wk	51/90 (57)	-	0	8 (9)
EVLA						
Proebstle *et al*., 2003a	41	1m	-	-	1/37 (3)	4/37 (11)
		6m	37/39 (95)	-	-	-
Ravi *et al*., 2006	101	2wk	92/101 (91)	-	0	-
		3y	34/37 (92)	-	-	-
Gibson *et al*., 2007	210	3d	210/210 (100)	-	12/210 (6)	-
		6wk	-	143/200 (71)	-	3/200 (2)
		4m	121/126 (96)	-	-	-
Thievacumar *et al*., 2007	68	6wk	68/68 (100)	56/68 (82)	0	3/68 (4)
		3m	68/68 (100)	-	-	-
		6m	48/48 (100)	-	-	0/48 (0)
Park *et al*., 2008	96	1m	89/93 (96)	-	0	4/95 (4)
		1y	77/77 (100)	-	-	0/77 (0)
		3y	55/55 (100)	-	-	-
Huisman *et al*., 2009	169	3m	148/150 (98)	-	0/150 (0)	2/150 (1)
Kontothanassis *et al*., 2009	229	1wk	227/229 (99)	-	3/229 (1)	5/229 (2)
		1y	147/154 (95)	-	-	0/154 (0)
Desmyttere *et al*., 2010	147	1wk	147/147 (100)	-	0	58/147 (40)
		1y	114/117 (97)	117/117 (100)	-	0
		3y	30/30 (100)	30/30 (100)	-	-
Doganci *et al*., 2011	68	1wk	68/68 (100)	-	0	7/68 (10)
		6m	68/68 (100)	-	-	0/68 (0)
RFA						
Merchant *et al*., 2005	52	1wk	-	-	-	(9)
		6m	-	-	-	(10)
UGFS						
Darke and Baker, 2006	28	6wk	27/27 (100)	-	-	-
Coleridge Smith, 2006	263	6m+	116/141 (83)	132/141 (94)	-	0
Myers *et al*., 2007	177	3y	(36)	-	-	-

Figures in parentheses are percentages

More recently EVLA and RFA have been used to reduce morbidity, allow faster return to normal activities, and to be at least as effective as traditional SVS. Early occlusion rates following EVLA to the SSV range from 91 to 100% (**Table 2.4**), (Ravi *et al*., 2006; Gibson *et al*., 2007; Theivacumar *et al*., 2007; Park *et al*., 2008; Huisman *et al*., 2009; Kontothanassis *et al*., 2009; Desmyttere *et al*., 2010; Doganci *et al*., 2011) and the limited data available suggest this is sustained to six months (95-100%) (Proebstle *et al*., 2003a; Gibson *et al*., 2007; Theivacumar *et al*., 2007; Park *et al*., 2008; Kontothanassis *et al*., 2009; Desmyttere *et al*., 2010; Doganci *et al*., 2011) and even to three years (92-100%). (Ravi *et al*., 2006; Park *et al*., 2008; Desmyttere *et al*., 2010) Two studies reported an absence of visible VV in 71% and 82% of patients at six weeks after EVLA, (Gibson *et al*., 2007; Theivacumar *et al*., 2007) and one study found no recurrence of visible SSVV at 1 or 3 years. (Desmyttere *et al*., 2010) Early paraesthesia rates range from 0 to 40%, (Proebstle *et al*., 2003a; Gibson *et al*., 2007; Theivacumar *et al*., 2007; Park *et al*., 2008; Huisman *et al*., 2009; Kontothanassis *et al*., 2009; Desmyttere *et al*., 2010; Doganci *et al*., 2011) all of which resolved by six month follow-up.

The vast majority of studies of RFA for VV have concentrated on GSV treatment. Merchant *et al*. treated 52 SSV with RFA, however they combined duplex and clinical outcomes for both GSV and SSV. (Merchant *et al*., 2005) They found paraesthesia in 9% of limbs in which the SSV had been treated at 1 week, and 10% at 6 months (**Table 2.4**).

Three other groups have also published their results on UGFS outcomes for SSV treatment since this study began (**Table 2.4**). Darke and Baker found a 100% occlusion rate at six weeks in 27 limbs, but they did not look at longer term results

and half of the patients only had direct injections into varicosities as the distal SSV trunks were small and competent. (Darke and Baker, 2006) Coleridge Smith found SSV occlusion in 83% of limbs followed up for longer than six months, but unfortunately those attending follow-up only represented less than 60% of the treated cohort. (Coleridge Smith, 2006) In contrast with these reports and the current study, Myers *et al.* found a worse outcome in SSV UGFS compared with GSV UGFS; only 36% occlusion at three years, although some patients were treated with liquid sclerosant only, some had tributary rather than truncal injections, and various types and concentrations of sclerosant were used. (Myers *et al*., 2007) Paraesthesia is not a documented complication of UGFS, and the incidence of DVT is fairly similar (0-5%) with all modes of treatment (**Table 2.4**). (Van Rij *et al*., 2004)

The occlusion rates seen in the current study after UGFS are better than those seen in the literature after conventional SVS. (**Table 2.4**) Paraesthesia rates are also lower. The results of the current study are similar to those found with EVLA, although the medium to long-term recanalisation rate is probably slightly higher with UGFS, however, subsequent UGFS is no more technically difficult than the initial procedure and is usually effective. It is also important to remember that anatomical failure does not necessarily result in clinical recurrence.

EVLA and RFA only replace the 'stripping' part of SVS and in addition the remaining tributary varicosities often have to be treated either by sclerotherapy or phlebectomy, thereby increasing treatment time and costs. (Merchant *et al*., 2005; Mundy *et al*., 2005; Pannier and Rabe, 2006; Darwood *et al*., 2008) EVLA also requires a >10cm relatively straight segment of SSV immediately distal to the SPJ and the absence of severe varicosities arising within 5cm of the SPJ. (Theivacumar *et al*., 2007) Indeed,

only 70% of consecutive patients with SSV incompetence were suitable for EVLA in one study. (Theivacumar *et al*., 2007) For UGFS no such requirements are necessary with the only limiting factor being the experience of the operator. Indeed in the current study, no patients were turned down for UGFS for symptomatic SSV incompetence.

In this study, 14 patients were treated for recurrent SSVV after previous SSV surgery, and none of these had developed a recurrence by 12 months. UGFS would be particularly suitable for recurrent SSVV where the anatomical requirements for EVLA may not be met, and SVS is more technically demanding and associated with higher complication rates.

Patient attendance at clinical and duplex follow-up in this study was very good with 100%, 97% and 95% of patients attending follow-up at 1, 6 and 12 months respectively. This is unusually high for patients undergoing treatment for VV, but may in part be explained by the fact that patients were attending a dedicated research clinic and were not kept waiting, and also that follow-up was often arranged at a time to suit them. The patients may also have been more motivated to attend as they knew they were undergoing a new treatment of which the long-term outcomes were uncertain, and they were getting closer follow-up than is usually available on the NHS. No financial assistance or incentives were given.

In conclusion, UGFS is an effective treatment for SSV incompetence in terms of occlusion of the treated vein and abolition of reflux and the disappearance of visible VV. Longer term follow-up is required to determine the durability of UGFS, although repeat treatments are quick, easy, effective and well-tolerated.

2.4 Ultrasound-guided foam sclerotherapy for the treatment of chronic venous ulceration: a preliminary study

The data contained within this Chapter were

- presented (poster) at the West Midlands Surgical Society in Birmingham, UK in May 2009
- published in the European Journal of Vascular and Endovascular Surgery in May 2009 (Darvall *et al*., 2009c).

2.4.1 Introduction

Approximately 1% of Europeans will develop CVU during their life time; the point prevalence of open ulceration is estimated at 0.1%. (Nelzen *et al*., 1996; Margolis *et al*., 2002; Ruckley *et al*., 2002) CVU has a significant adverse impact on HRQL and the condition consumes significant health care resources. (Phillips *et al*.,1994; Ruckley, 1997; Kurz *et al*., 1999)

The treatment of CVU remains controversial and outcomes are often disappointing, especially in the presence of DVR. However, one RCT (ESCHAR) comparing compression alone with compression plus SVS in patients with SVR and CVU found that, although there appeared to be no difference in healing rates, recurrence rates were significantly lower in the SVS group. (Barwell *et al*., 2004) Only one group has published data to suggest that UGFS in patients with CVU and SVR may be an effective and attractive alternative to SVS in this often elderly and frail population.

(Cabrera *et al*., 2004) However, the study was retrospective and did not include DUS follow-up to assess residual or recurrent reflux and its relationship with CVU healing.

The aim of this study, therefore, is to describe prospectively the rate of CVU healing and recurrence during the 12 months following UGFS of SVR, and also to assess the relationship between healing, recurrence and the pattern and severity of post-intervention venous reflux as determined by serial DUS.

2.4.2 Methods

2.4.2.1 Patients

Following local ethical committee approval and obtaining written informed consent, consecutive patients undergoing UGFS in addition to compression bandaging as part of their treatment for open (CEAP clinical grade 6) CVU between June 2005 and May 2007 were invited to take part in the study (as per **Section 2.1.2.1**).

To be considered suitable for inclusion patients had to have open (CEAP C_6) CVU, and significant reflux (>0.5s) in the GSV or SSV confirmed on DUS. Patients without SVR, those with an ABPI <0.8 or post-thrombotic deep venous occlusion, and those in whom the ulcer had healed prior to UGFS treatment were excluded.

2.4.2.2 Pre-treatment assessment

Patients were examined and the severity of venous disease according to the CEAP clinical classification was determined (**Table 1.1**).

DUS was performed, as described in **Section 2.1.2.2**, at the initial clinic attendance in order to identify sites of superficial, deep and communicating venous reflux. At this appointment, an ulcer history was also taken and the ABPI was measured.

2.4.2.3 Management of CVU while awaiting UGFS treatment

Patients were put on the waiting list for UGFS (approximately four to six weeks) and the ulcerated limb was placed into multilayer compression bandaging, using Profore® or ProGuide® (Smith and Nephew, Hull, UK) delivering 40 mmHg at the ankle, while awaiting treatment.

2.4.2.4 UGFS treatment

UGFS treatment was performed as described in **Section 2.1.2.3**, with the following modifications.

As previously described, a roll of Velband® was applied directly along the treated saphenous trunk and was retained on the thigh using Pehahaft® cohesive bandage. Below-knee multilayer compression bandaging was applied using Profore® or ProGuide®, and a thigh-length class II compression stocking (with the foot/lower leg portion removed) was applied over the top. The thigh bandaging was left in place for seven to ten days when the patient was reviewed in clinic, at which time the bandaging was removed and the class II stocking worn (along with the below-knee multilayer compression bandaging) for a further three weeks. Compression

bandaging was changed by the district nurse as necessary according to the amount of exudate.

2.4.2.5 Outcome measures and follow-up

The chosen outcome measures were ulcer healing and complete occlusion of, and abolition of reflux in, the treated saphenous trunks on DUS.

Patients were followed up at 7-10 days and one, six and 12 months as described in **Section 2.1.2.4** with DUS and clinical examination. At the first visit the bandages were removed and DUS was performed specifically to look for DVT.

Ulcer healing was defined as complete re-epithelialisation of the leg, and ulcer recurrence as any loss of skin continuity below the knee.

After ulcer healing was achieved patients wore below-knee class II stockings (Medi, Hereford, UK) and patients were advised to wear these during the daytime.

2.4.3 Results

2.4.3.1 Patients

Twenty-seven patients (28 limbs) of median age 69 (interquartile range [IQR] 54-79) years with open CVU of primary aetiology (CEAP C6, E_P) were treated between June 2005 and May 2007. Demographic data, ulcer history, and pre-UGFS findings on DUS are shown in **Table 2.5**. ABPI was normal (>0.8) in all limbs. SVR alone (A_S)

was present in 20 limbs and eight limbs had mixed SVR and DVR (A_{SD}); all limbs had reflux (P_R) rather than obstruction.

Table 2.5 Ulcer pre-treatment data

Demographics			Ulcer characteristics			Refluxing segments on duplex†		
Patient	Gender	Age	Site	Duration	Compression‡	DV	GSV	SSV
1	F	87	Lateral	10y	+	+	-	+
2	M	86	Medial	12m	+	+	+	-
3	F	67	Medial	6m	-	-	+	-
4	M	22	Medial	2y	-	-	+	-
5	M	58	Medial	9m	-	-	+	-
6	F	53	Medial	9m	+	-	+	-
7	F	74	Lateral	4m	+	-	+	-
8	F	56	Medial	9y	+	-	+	-
9	M	79	Medial	4y	-	-	+	-
10	F	70	Medial	6m	-	+	-	+
11	F	56	Medial	4y	+	+	+	-
12	F	89	Medial	3m	-	-	+	-
13	M	68	Medial	12m	+	+	+	-
14	M	62	Medial	12m	-	-	+	-
15	F	55	Lateral	2y	+	-	+	-
16	F	80	Lateral	12m	+	-	+	-
17	M	52	Medial	6m	-	-	+	-
18	F	38	Medial	7m	-	-	+	-
19	M	86	Medial	40y	+	-	+	
20	M	49	Lateral	12m	-	-	+	-
21	M	79	Medial	20m	-	-	+	-
22	F	75	Lateral	4m	-	+	+	-
23	F	81	Medial	8m	-	-	+	-
24	M	51	Medial	12m	+	-	+	-
25	M	70	Medial	12m	+	+	+	-
26	F	79	Medial	3m	-	+	+	+
27-R	F	54	Lateral	12m	-	-	+	-
27-L	F	54	Lateral	12m	-	-	+	-

† + = reflux present; - = no reflux. DV = deep veins (superficial femoral and or popliteal vein); ‡ + = compression bandaging used to treat current ulcer; - = no compression tried

Four patients had a previous history of DVT; this was multiple in two patients and they consequently were on lifelong warfarin, one with a target INR of 4.5, the other 3.5. Two other patients were on warfarin for atrial fibrillation with target INR of 2-3. Median ulcer duration (IQR) was 12 (6-23) months.

There were no symptomatic DVT in any of the treated limbs, neither was there evidence of DVT on DUS at seven-ten days or one, six or 12 month follow-up. There were no episodes of visual disturbance or other neurological symptoms, no cutaneous ulceration at cannulation sites, or paraesthesia.

2.4.3.2 Ulcer healing

At one and six months after treatment with a median of 8ml foam (range 2-14ml), 22 ulcers (79%) and 27 ulcers (96%) respectively had healed completely (**Table 2.6, Figure 2.12**). Although the patients were not seen personally by the investigators at hospital between one and six months, all were reported by community carers to have healed their ulcers within three months of treatment. One patient whose ulcer had not healed at one month died soon after from carcinomatosis and was, therefore, excluded from further analysis. At 12 months, 25 ulcers (93%) remained healed and two ulcers had recurred (7%). Both patients who had recurrence at 12 months had stopped wearing their compression stockings, and both also had DVR prior to (and after) treatment.

2.4.3.3 Treated vein occlusion

Total occlusion of all treated veins at one month was observed in 22 of 28 limbs (**Table 2.6, Figure 2.12**).

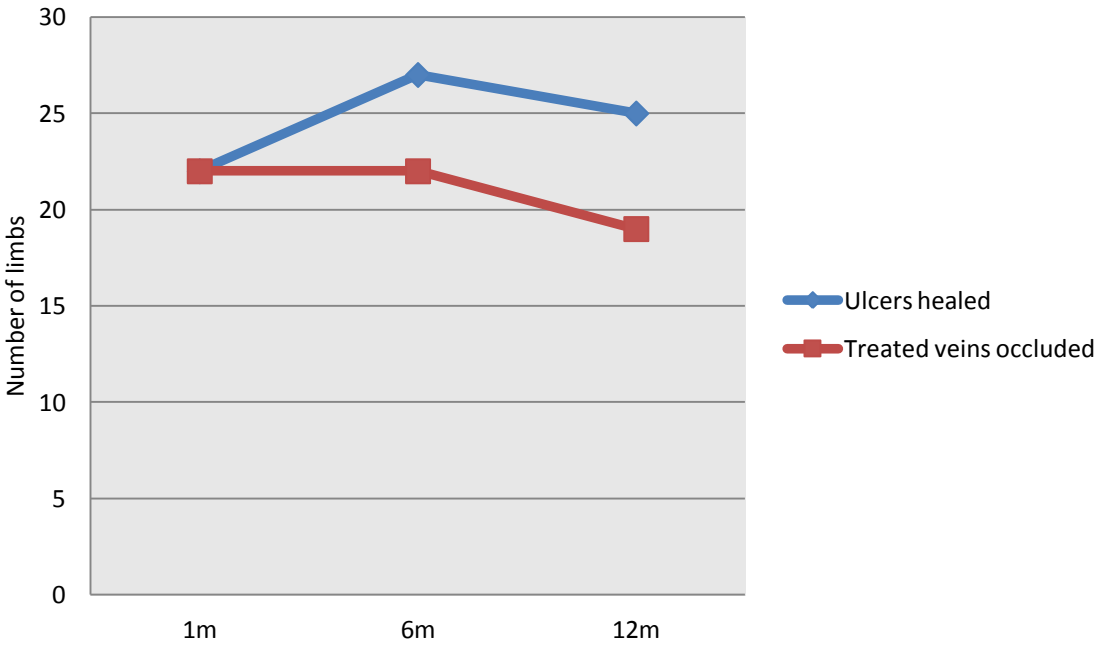
Table 2.6 Ulcer treatment and follow-up data

	Treatment data		Ulcers completely healed at follow-up†			All treated venous segments occluded on follow-up duplex scan‡		
Patient	No. of cannulae	Volume of foam (ml)	1m	6m	12m	1m	6m	12m
1	1	2	+	+	+	+	+	+
2	1	12	+	+	+	-	-	-
3	1	8	+	+	+	+	+	-
4	2	12	+	+	+	+	+	-
5	1	8	+	+	+	+	+	+
6	2	10	+	+	+	+	+	+
7	3	8	-	+	+	+	+	+
8	2	12	-	+	+	+	+	+
9	2	8	+	+	+	-	+	+
10	2	8	+	+	+	+	+	+
11	2	8	-	+	-	-	-	-
12	1	8	+	+	+	+	+	+
13	2	10	+	+	+	+	+	+
14	2	10	+	+	+	+	+	+
15	1	8	+	+	+	+	+	-
16	2	8	+	+	+	+	+	+
17	1	8	-	+	+	+	+	+
18	2	10	+	+	+	-	+	+
19	1	4	-			-		
20	1	8	+	+	+	-	-	-
21	2	12	-	+	+	+	+	+
22	1	3	+	+	-	+	+	+
23	1	8	+	+	+	+	-	-
24	3	10	+	+	+	+	+	+
25	2	8	+	+	+	+	+	+
26	4	14	+	+	+	+	-	-
27-R	2	10	+	+	+	+	+	+
27-L	1	6	+	+	+	+	+	+

† + = completely healed; - = not healed; left blank = lost to follow-up (died).
‡ + = all treated venous segments occluded and no residual reflux; - = some reflux present; left blank = lost to follow up (died)

Two patients had had unsuccessful treatment: one refused further treatment (patient 19) and the other had repeat UGFS although the ulcer was already healed (patient 18). Three patients had residual BK-GSV reflux only with an occluded GSV in the thigh (patients 2, 9 and 20). All of these patients' ulcers had healed by one month and only one wanted further treatment (patient 9) for residual visible VV. The remaining one patient (patient 11) only had occlusion of her proximal GSV after the first treatment with many remaining VV and distal reflux. Her previously almost circumferential ulcer however was much improved and she did not want further injections.

Figure 2.12 Ulcer healing rates and treated vein occlusion rates after UGFS



At six month follow-up 22 of 27 limbs (patient 19 lost to follow-up) had total occlusion of all treated veins. Patients 2 and 20 still had residual BK-GSV reflux and patient 11

still only had occlusion of the proximal GSV. The remaining two patients had had recanalisation of their BK-GSV with recurrent reflux (patients 23 and 26). In both patients the ulcers remain healed and they only had a few VV so no further treatment was wanted.

At 12 months, 19 of 27 limbs had total occlusion of all treated veins. The situation for patients 2 and 20 (residual BK-GSV reflux) and patients 23 and 26 (recurrent BK-GSV reflux) remained unchanged. Patients 3, 4 and 15 had recanalisation of the majority of their GSV with recurrent reflux at 12 months follow-up. However, their ulcers remained healed and they had few visible VV and remained asymptomatic, so they elected to have no further treatment at this stage. Finally, patient 11 had a recurrence of her ulcer between 6 and 12 months and continued to have distal reflux and many VV amenable to treatment with UGFS. However, the ulcers are intermittent and her symptoms are much improved so she continues to decline further treatment.

2.4.4 Discussion

The main findings of the present study are that following UGFS combined with compression, 27 of 28 (96%) CVU healed within three months, and at 12 months only two ulcers had recurred.

The outcomes reported here appear superior to those reported from other studies using compression alone with no attempt made to eradicate SVR (healing 68-83% at six months, recurrence 26-28% at 12 months). (Bello *et al*., 1999; Barwell *et al*., 2000; Ghauri *et al*., 2000)

The importance of eradicating SVR was clearly demonstrated in the ESCHAR study, an RCT of 500 patients comparing CVU healing and recurrence rates with compression bandaging alone, and following SVS combined with compression. (Barwell *et al*., 2004) Healing rates at six months were 65% in both groups, and approached 80% by 12 months. (Barwell *et al*., 2004) Recurrence rates, however, were significantly lower in patients undergoing SVS, 15% *versus* 34% at a median follow-up of 14 months (range 10-23 months). (Barwell *et al*., 2004) Longer term follow-up from the same study found CVU healing rates at three years of 89% in the compression only group, and 93% in the SVS and compression group (P = .73, log rank test); and CVU recurrence rates at four years of 56% in the compression only group, and 31% for the SVS and compression group (P < .01). (Gohel *et al*., 2007)

The CVU outcomes reported here after UGFS appear to be at least as good as those reported after SVS in the ESCHAR study (n=216), although the numbers in the studies are very different. This suggests that UGFS may be an attractive alternative to SVS in this group of patients who are often elderly, frail and refuse (or are refused) operative intervention; further supporting this is the lack of side-effects found in this clinical series and the successful treatment of four patients anticoagulated with warfarin. Four other groups have thus far looked at the effect of UGFS on CVU healing and have also reported promising results.

In 2004, Cabrera *et al.* reported a retrospective study of 116 consecutive patients with 151 CVU of median duration (range) 62 (1-480) months treated over a ten-year period with 0.27% to 1% polidocanol CO_2 microfoam. Almost 30% of their patients had DVR and 20 had undergone previous SVS (unspecified). Unlike the present study where only two of the 28 treated limbs required two sessions of UGFS, their

patients underwent repeated treatment sessions (median 3.6, range 1-17) until all identifiable SVR was eliminated. At six months, Cabrera reported an 82.8% healing rate (96/116) with a median time to healing of 2.7 months; seven patients were never healed, one patient was lost to follow-up and there were recurrences in ten patients (9%). In a multivariate analysis they found that both long CVU duration and the presence of DVR were adverse prognostic factors; the latter appears to be the case in the present series too. Beyond six months, follow-up rates were really too low to undertake proper analysis of longer term healing and recurrence rates; and repeated post-intervention DUS scans to assess the success of their treatment were not undertaken. However, the authors reasonably concluded on the basis of their short term results that microfoam treatment of CVU was promising and worthy of further study. (Cabrera *et al*., 2001; Cabrera *et al*., 2004)

In 2006, Bergan *et al.* described their experience of 50 limbs with active CVU. Twenty-two were treated with compression bandaging alone, 13 failed compression therapy and went on to have UGFS, and a further 15 were treated promptly with UGFS. (Bergan *et al*., 2006) Polidocanol foam was used in strengths of 1-3%, and the usual volume used was 8ml. At six weeks follow-up they found complete CVU healing in 45% of the compression only group, and 100% of the patients who had had UGFS. (Bergan *et al*., 2006)

Hertzman *et al*. performed UGFS of incompetent GSV using 3% polidocanol in 13 legs with CVU (9 patients). At one week follow-up, they reported healing of two ulcers and improvements in another nine. (Hertzman and Owens, 2007) O'Hare and Earnshaw randomized 22 patients to compression bandaging alone and 18 patients to compression bandaging with additional UGFS using 3% STS. (O'Hare and

Earnshaw, 2010) They reported healing in 17/20 (85%) of the compression group, and 12/13 (92%) of the additional UGFS group at 24 weeks. Unfortunately the study failed to recruit and randomize the 170 patients required for formal comparison.

It has been suggested that this observed increased efficacy of UGFS over SVS in CVU healing could be due to the fact that the foamed sclerosant can act directly on the microcirculation (the end point of venous hypertension), rather than indirectly by superficial venous stripping. (Pascarella *et al*., 2006; Hertzman *et al*., 2007)

Also, GSV stripping is usually carried out to knee level only due to the risk of damage to the saphenous nerve below the knee, (Morrison and Dalsing, 2003) with 44-91% of patients having reflux in the BK-GSV at two-year follow-up. (MacKenzie *et al*., 2002b; MacKenzie *et al*., 2004; Blomgren *et al*., 2005; van Neer *et al*., 2009) Kulkarni *et al.*, however, concluded that residual reflux after SVS is not the most important predictor of CVU recurrence, and although the hazard ratio of developing CVU recurrence by three years was 2.5 in those with residual BK-GSV reflux, this did not reach statistical significance. (Kulkarni *et al*., 2007) No other group has considered the effect of technically 'successful' treatment (i.e. occlusion of all treated veins on duplex) on CVU healing and recurrence. In the current study, of the three patients who still had residual reflux in the thigh GSV at one month, only one ulcer had healed. Five limbs have had some recurrence of reflux by 12 months but in none of these limbs have the ulcers recurred. It will be interesting to see whether these patients go on to develop recurrent CVU and hence whether it would be useful to treat these asymptomatic 'recurrences' to prevent this. Of the two patients with recurrent CVU, both have DVR and one continued to have significant SVR also.

The small number of patients is an inherent weakness in the study, but as a preliminary study it demonstrates the potential of UGFS as an adjunct to healing CVU. The results must be interpreted with caution due to the fact that only 12 of 28 limbs had been treated by compression prior to assessment for treatment. This is slightly offset by the observation that none of the ulcers healed in the interval between placement on the waiting list for treatment and attending for UGFS (usually four to six weeks), during which time all limbs were treated with multilayer graduated compression bandaging. Another obvious limitation is that this study is not an RCT. Although all patients are offered a choice between SVS and UGFS as appropriate, in our practice patients rarely choose a surgical option. The striking differences we have observed over the last few years between the outcomes following UGFS and SVS have removed our 'grey area of clinical equipoise' and we therefore feel it inappropriate for us to randomise patients between the two treatments. Even if we did wish to do that type of study, it is clear that the great majority of our patients would simply refuse randomisation. In these particular patients, this problem of recruitment and suitability for treatment has been demonstrated in the published RCTs. (Howard *et al*., 2008; O'Hare and Earnshaw, 2010)

In summary, our preliminary data add further weight to the contention that eradication of SVR by means of UGFS improves CVU outcomes when compared to compression alone. In this regard, UGFS appears to be at least as effective as SVS as a means of dealing with SVR and does, therefore, appear the more attractive option in this elderly patient population. As is probably to be expected, patients with DVR do not respond as well to treatment with UGFS but this is also true of SVS and compression alone. Furthermore, the novel follow-up duplex data presented here does suggest

long-term healing following UGFS probably requires careful follow-up and, if required, further sessions of UGFS to make sure that SVR remains completely eradicated.

CHAPTER 3. THE SAFETY AND ACCEPTABILITY OF ULTRASOUND-GUIDED FOAM SCLEROTHERAPY

As well as being effective, the ideal treatment for VV should be free from complications and allow a quick return to work and normal activities. While SVS is the traditional gold standard for the treatment of VV, it is not complication-free and can be associated with a prolonged recovery. UGFS, to be considered a useful alternative, should be associated with less morbidity and a quicker recovery.

In this Chapter I compare the safety and acceptability of UGFS compared with SVS in terms of post-procedural morbidity and time taken to return to normal activities.

3.1 Recovery and return to normal activities after ultrasound-guided foam sclerotherapy compared with conventional surgery for varicose veins

The data contained within this Chapter were

- presented (poster) at the International Surgical Congress of the Association of Surgeons of Great Britain and Ireland in Glasgow, UK in May 2009
- published in the British Journal of Surgery in November 2009 (Darvall *et al*., 2009a).

3.1.1 Introduction

Surgical treatment of VV improves physical symptoms, generic and disease-specific HRQL, and venous haemodynamics. (Smith *et al*., 1999; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam *et al*., 2004a) However, it is also widely accepted that such surgery can be associated with a significant incidence of complications, morbidity, and delayed return to normal activities and to work. (Sam *et al*., 2004b; van Rij *et al*., 2004; Beale and Gough, 2005; Subramonia and Lees, 2005; Wood *et al*., 2005)

Apart from being unpleasant for some patients and a rich source of medicolegal activity, (Tennant and Ruckley, 1997; Ray, 2005) adverse outcomes after SVS can have a significant financial impact in this predominantly young and economically active patient population. Minimally invasive techniques may have advantages over

traditional SVS that include less morbidity and quicker return to normal activities. (Beale and Gough, 2005)

The aim of this study, therefore, is to determine early morbidity, analgesia use, and time taken to return to driving and work following UGFS, and to compare these findings with those in a contemporaneous series of similar patients undergoing SVS.

3.1.2 Methods

3.1.2.1 Patients

Local ethical committee approval and written informed consent was obtained from all patients. Questionnaires were posted to 391 consecutive patients who had UGFS between November 2004 and May 2007, and 94 consecutive patients who had conventional SVS between October 2007 and March 2008. All patients were treated at HEFT but under the care of separate surgical teams. All patients were referred by their general practitioners to NHS outpatient clinics, and were assessed in a consultant-led vascular outpatient clinic.

To be considered for treatment patients had to have symptomatic, CEAP C_{2-6} venous disease (i.e. treatment was not offered for cosmetic indications) and significant (>0.5s) reflux in either the GSV or SSV.

3.1.2.2 Pre-treatment assessment

Patients were examined and the severity of venous disease according to the CEAP clinical classification was determined (**Table 1.1**).

DUS was performed, as described in **Section 2.1.2.2**, at the initial clinic attendance in order to identify sites of superficial, deep and communicating venous reflux.

3.1.2.3 UGFS treatment

UGFS treatment was performed as described in **Section 2.1.2.3**. In patients with bilateral VV only one leg was treated at a time (worst leg first); the second leg was treated at least four weeks later. UGFS patients were told to take analgesia as required, to return to driving when they felt able to perform an emergency stop, and to return to work when they felt comfortable. It was suggested to patients who had had their right leg treated that they wait until the bandaging was removed to commence driving as it may prove difficult to perform an emergency stop.

3.1.2.4 Surgical treatment

All SVS was performed on inpatients, usually without an overnight stay, under general anaesthesia. Patients with bilateral VV usually had both legs treated at the same time. Primary GSV incompetence was treated by SFJ ligation, stripping of the GSV to knee level and multiple stab phlebectomies. Recurrent GSV varices were treated by re-exploration at the groin, and phlebectomies with stripping of any GSV remnant, as appropriate. SSV incompetence was treated by SPJ ligation (marked immediately before operation by DUS), removal of the proximal 10cm of the SSV via

the popliteal incision, and phlebectomies. No surgeon performed stripping of the SSV.

Limbs were bandaged after SVS with Velband® and Elastocrepe® (Smith and Nephew Healthcare, London, UK). Bandaging was replaced after 24 hours with thigh-length antiembolism stockings (TED®; Kendall Healthcare Products, Mansfield, MA) worn for a further two weeks. No specific restrictions were suggested to patients. They were advised to take analgesia as required, to return to driving when they felt able to perform an emergency stop, and to return to work when they felt comfortable.

3.1.2.5 Questionnaires and outcome measures

Questionnaires (**Appendix 3 and 4**) were sent to all patients four weeks after treatment. No reminders were sent. Separate questionnaires were sent for each treated leg. Patients were asked to grade the amount of pain, bruising, itching and lumpiness they had following UGFS or SVS. Possible responses were ‘an awful lot’, ‘a lot’, ‘quite a bit’, ‘a little’ or ‘none’. ‘An awful lot’ and ‘a lot’ were grouped together, as were ‘a little’ and ‘none’ for analysis. Patients were also asked: ‘For how many days after your foam injections/varicose vein surgery did you take painkilling tablets?’ Possible responses were: ‘none at all’, ‘same day only’, ‘1-2 days’, ‘2-4 days’, ‘5-7 days’, ‘7-14 days’ and ‘more than 14 days’. The final questions were: ‘How long after your foam injections/varicose vein surgery did you return to work/driving?’ Possible responses were: ‘I don’t go out to work/drive’, ‘same day’, ‘next day’, ‘2-7 days’, ‘7-14 days’ and ‘more than 14 days’.

3.1.2.6 Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 software (SPSS Inc., Chicago, IL, USA). The chi-squared test (X^2, with Yates' correction where appropriate) was used to compare proportions between the two groups. Analysis of return to work and driving, and analgesia use was undertaken for the group as a whole, and then again after exclusion of patients who had bilateral SVS.

3.1.3 Results

3.1.3.1 Patients and treatments

The response rates were 84.9% (332 patients, 418 limbs) in the UGFS group and 56% (53 patients, 70 limbs) in the SVS group. There were no significant differences between the groups in terms of age, sex, proportion with bilateral or recurrent VV, or extent of SVR treated (**Table 3.1**).

In the SVS group, four legs had primary SPJ ligation and phlebectomies; four legs had primary combined SFJ and SPJ ligation, GSV stripping and phlebectomies; four legs had groin exploration for recurrence and phlebectomies without GSV stripping; and 58 limbs had SFJ ligation, GSV stripping and phlebectomies (nine recurrent). In the UGFS group, 341 had GSV treatment (90 recurrent) with additional AASV treatment in 22; 55 has SSV treatment (ten recurrent); and 22 had both GSV and SSV treatment (nine recurrent).

Table 3.1 Demographic data of patients with VV treated by UGFS or SVS

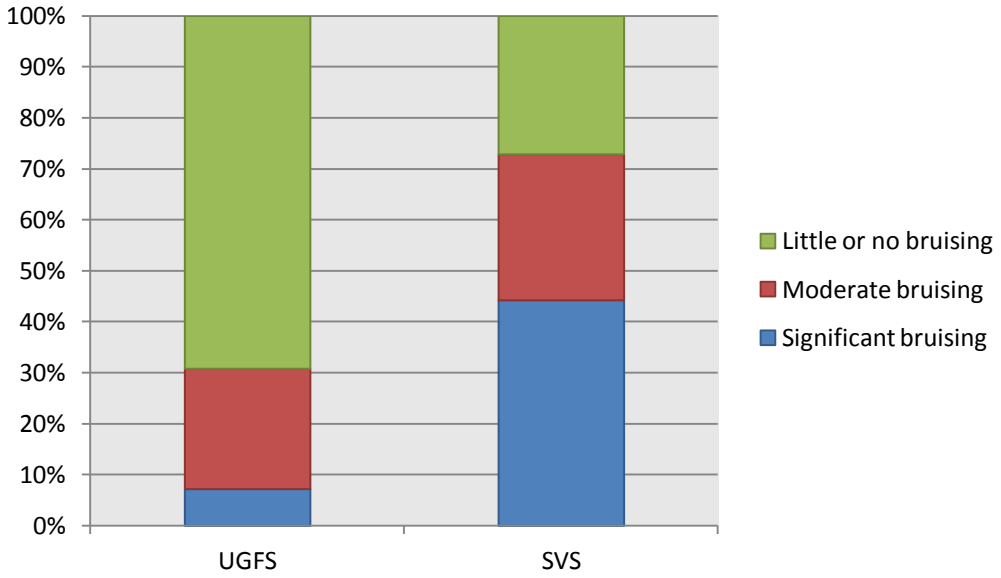
	UGFS	SVS	P
No. of patients	332	53	
No. of legs	418	70	
Age: median (IQR) in years	58 (46-66)	53 (42-64)	.162
Male sex[†]	111 (33.4)	20 (38)	.540
Bilateral[†]	87 (26.2)	17 (32)	.350
Recurrent[‡]	109 (26.1)	13 (19)	.085
GSV[‡]	363 (86.8)	66 (94)	.120
CEAP C2 or C3[‡]	296 (70.8)	57 (81)	.066

P values from chi-squared test, except age where MWU test was used
Values in parentheses are percentages of patients[†] or legs[‡] unless otherwise specified

3.1.3.2 Complications of UGFS

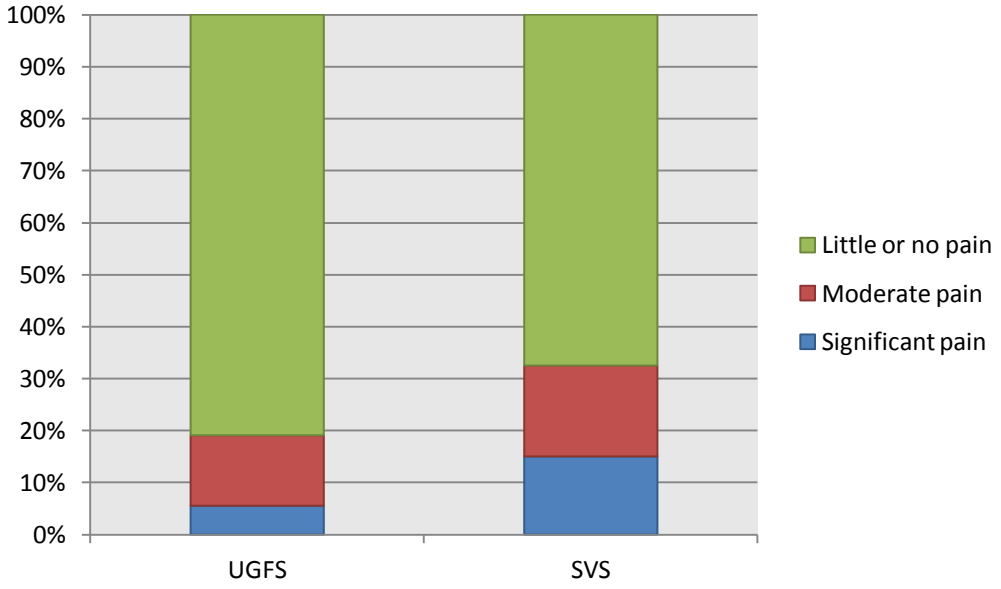
One symptomatic popliteal vein thrombosis was detected four days after UGFS, localized to the area of the SPJ. This was treated with warfarin for six months, at which point the patient was asymptomatic but had mild DVR. Three patients complained of visual disturbance following foam injections, consisting of blurred vision that lasted for less than 10 minutes. There were no other complications or adverse effects and, in particular, no other neurological symptoms or symptoms of nerve injury in the treated leg. Complications after SVS were not recorded.

Figure 3.1 Bruising following treatment



UGFS n=418; SVS n=70
Presence of significant bruising: UGFS *versus* SVS, 7.2% *versus* 44%, P < .0001, χ^2

Figure 3.2 Pain following treatment

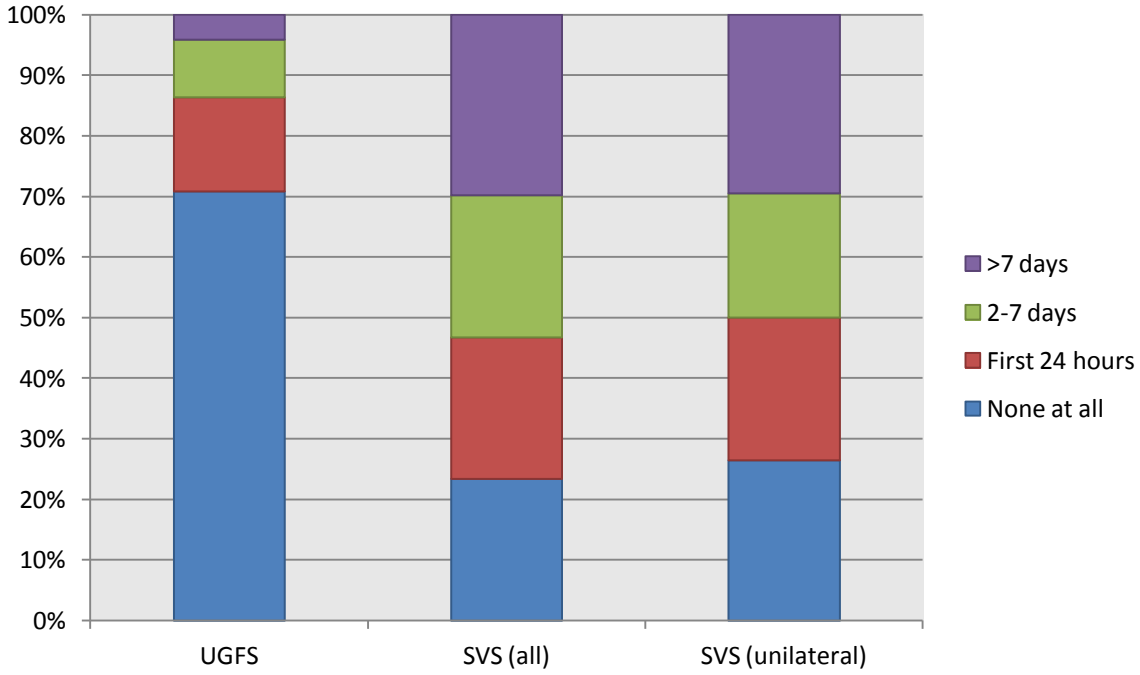


UGFS n=418; SVS n=70
Presence of significant pain: UGFS *versus* SVS, 5.5% *versus* 17%, P = .001, χ^2

3.1.3.3 Questionnaire results

Significant bruising (44% after SVS *versus* 7.2% after UGFS; P < .0001) (**Figure 3.1**) and pain (17% *versus* 5.5%; P = .001) (**Figure 3.2**) were significantly more common after SVS. There was no difference in terms of itching (SVS 10%, UGFS 8.4%) or lumpiness (SVS 9%, UGFS 7.4%).

Figure 3.3 Duration of analgesia usage following treatment



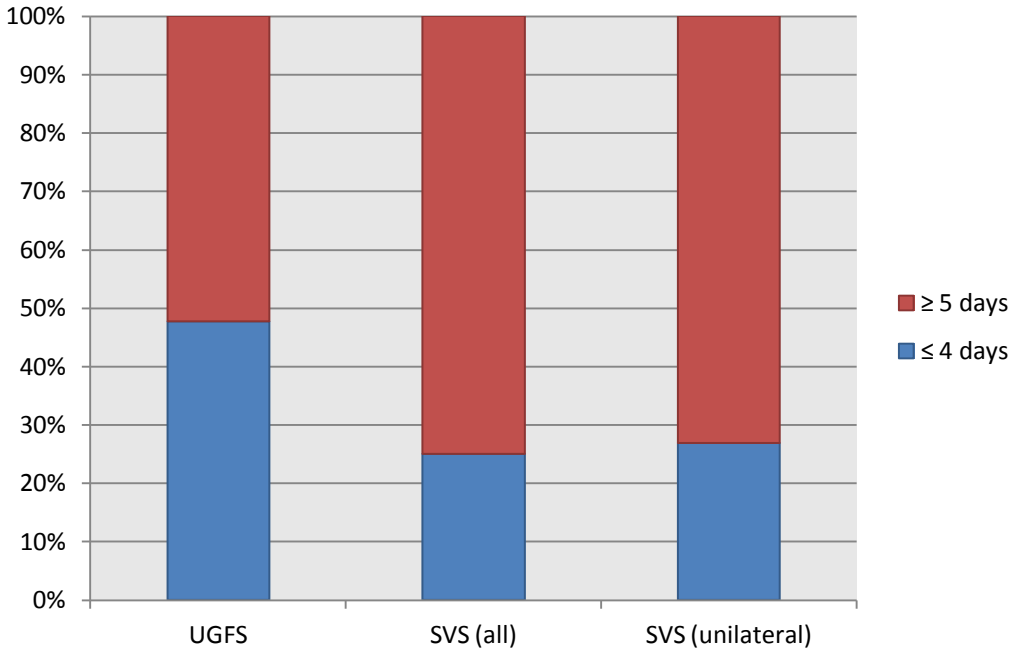
UGFS n=418; SVS (all patients) n=53; SVS (unilateral only) n=36
No analgesia at all:
UGFS *versus* SVS (all patients), 70.8% *versus* 23%, P < .0001, χ^2
UGFS *versus* SVS (unilateral only), 70.8% *versus* 26%, P < .0001
Analgesia usage for >1 week:
UGFS *versus* SVS (all patients), 4.1% *versus* 30%, P < .0001
UGFS *versus* SVS (unilateral only), 4.1% *versus* 29%, P < .0001

After UGFS, 70.8% of patients required no analgesia compared with 24% after SVS (P < .0001). After one week only 4.1% were still using analgesia compared with 30%

after SVS (P < .0001). These differences persisted when patients undergoing bilateral SVS were excluded from the analysis (**Figure 3.3**).

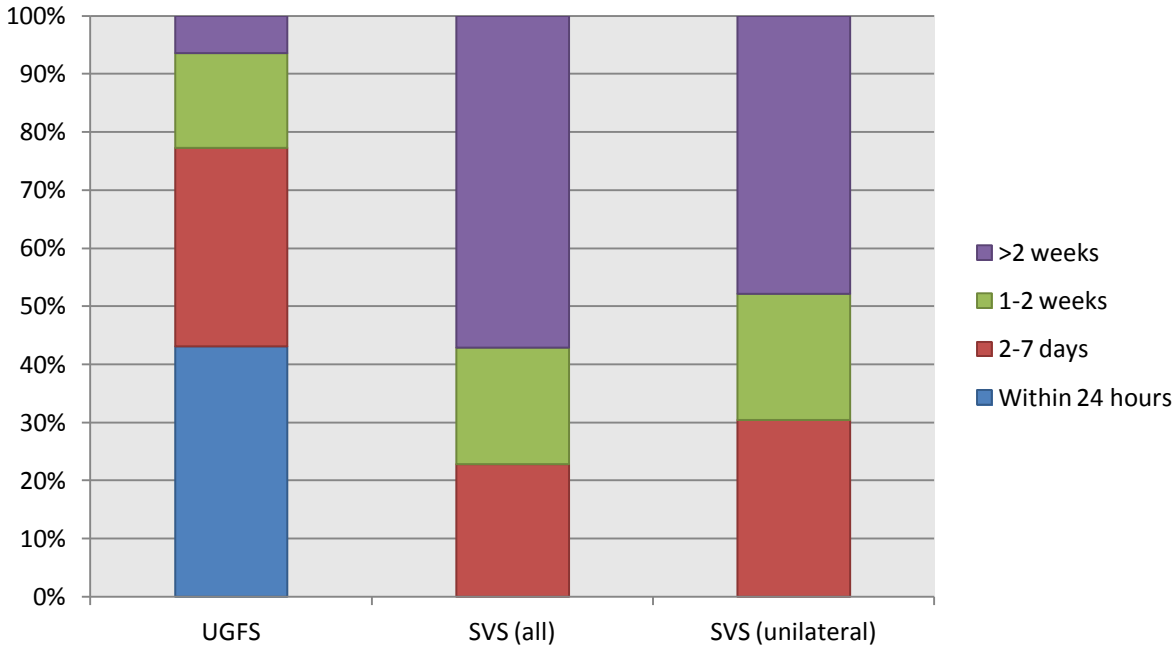
After UGFS, 47.7% of patients resumed driving within four days compared with 25% after SVS (P = .014) (**Figure 3.4**). After UGFS, 43.2% of patients returned to work within 24 hours, but none after SVS (P < .0001). Respective proportions after one week were 77.4% and 23% (P < .0001) (**Figure 3.5**). These differences in resuming driving and returning to work persisted when patients undergoing bilateral SVS were excluded from the analysis.

Figure 3.4 Time taken to return to driving following treatment



UGFS n=304 (114 non-drivers); SVS (all) n=32 (21 non-drivers); SVS (unilateral) n=26 (10 non-drivers)
Returned to driving within 4 days:
UGFS *versus* SVS (all), 47.7% *versus* 25%, P = .014, χ^2
UGFS *versus* SVS (unilateral), 47.7% *versus* 27%, P = .041

Figure 3.5 Time taken to return to work following treatment



UGFS n=234; SVS (all patients) n=35; SVS (unilateral only) n=23
Returned to work within 24 hours:
UGFS *versus* SVS (all patients), 43.2% *versus* 0%, P < .0001, χ^2
UGFS *versus* SVS (unilateral only), 43.2% *versus* 0%, P < .0001
Returned to work within 1 week:
UGFS *versus* SVS (all patients), 77.4% *versus* 23%, P < .0001
UGFS *versus* SVS (unilateral only), 77.4% *versus* 30%, P < .0001

3.1.4 Discussion

The main finding of this study is that when compared with conventional SVS, UGFS is associated with significantly less bruising, pain and analgesia requirement, and time off work and driving. UGFS is well-tolerated and safe, with only one DVT and three instances of self-limiting blurred vision after treatment.

Bruising after SVS has been reported in 25-53% of limbs which is similar to the incidence found in the current study. (Lurie *et al*., 2003; Subramonia and Lees, 2005) The incidence of bruising of 13-27% after RFA (Lurie *et al*., 2003; Vasquez *et al*.,

2007) and 11-15% after EVLA (Rasmussen *et al*., 2007; Christenson *et al*., 2010), while significantly less than after SVS, are still higher than the 7% rate of bruising after UGFS in the current study.

The levels of pain and analgesia use reported here after SVS are similar to those reported by others. (Nelzen, 2000; Shamiyeh *et al*., 2003; Biswas *et al*., 2007). Pain and tenderness have been found in several studies to be less common following RFA when compared with SVS (Rautio *et al*., 2002; Lurie *et al*., 2003; Hinchcliffe *et al*., 2006; Subramonia and Lees, 2010), being present in one study in 10% of RFA patients and 25% of SVS patients (Lurie *et al*., 2003). RFA patients also required less analgesia than patients having SVS (Rautio *et al*., 2002; Subramonia and Lees, 2010). In recently published RCTs, RFA has been found to be associated with significantly less pain and post-operative analgesia use than EVLA. (Goode *et al*., 2010; Shepherd *et al*., 2010a) After EVLA pain along the treated vein is reported in up to 50% of patients during the first week (Pannier and Rabe, 2006). However, results from the RCTs are somewhat inconsistent with two such studies finding no difference between EVLA and SVS in terms of pain scores and analgesia requirement (Rasmussen *et al*., 2007; Christenson *et al*., 2010); one finding in favour of EVLA (Carradice *et al*., 2011); and another in favour of SVS. (Pronk *et al*., 2010) In the current study we found significant pain in only 6% of patients undergoing UGFS and only 4% continued to require analgesia one week after treatment.

In the present study, return to work and driving was significantly quicker after UGFS than after SVS and appeared similar to, or perhaps better than, that reported after other minimally invasive treatments. The median time to return to work after SVS has been reported at between four and 21 days (Bountouroglou *et al*., 2006; Wright *et al*.,

2006a; Darwood *et al*., 2009; Subramonia and Lees, 2010; Pronk *et al*., 2010; Carradice *et al*., 2011). In one study, 10% of SVS patients took between six and 12 weeks to return to work (Biswas *et al*., 2007). Patients who had experienced minor complications, such as wound infection or haematoma, took even longer. (Wright *et al*., 2006a) Two studies found return to driving after SVS at a median of seven days, (Darwood *et al*., 2009; Subramonia and Lees, 2010) and median time to return to normal activities varies from 7-14 days. (Bountouroglou *et al*., 2006; Subramonia and Lees, 2010; Christenson *et al*., 2010; Carradice *et al*., 2011). Bilateral SVS had no effect on return to work and physical activity in one study (Shamiyeh *et al*., 2003), a finding supported by the current study, but in another those patients undergoing bilateral SVS took longer to return to work. (Darwood *et al*., 2009)

It has been suggested that, for the procedure to be cost-effective, patients undergoing RFA must return to work 3.2 days earlier than those having SVS. (Rautio *et al*., 2002) Reported median return to work following RFA ranges from 1.4 to 10 days (Rautio *et al*., 2002; Lurie *et al*., 2003; Beale and Gough, 2005, Subramonia and Lees, 2010), and RCTs found a significantly faster return to normal activities, driving and to work in patients undergoing RFA compared with SVS (Lurie *et al*., 2003; Subramonia and Lees, 2010). Again the situation with EVLA is less clear; two RCTs comparing RFA and EVLA found no differences in time to return to normal activities and to work between the groups, (Goode *et al*., 2010; Shepherd *et al*., 2010a) and three found no difference between EVLA and SVS; (Rasmussen *et al*., 2007; Pronk *et al*., 2010; Christenson *et al*., 2010) whereas others found recovery to be significantly quicker after EVLA compared with SVS. (Ravi *et al*., 2006; Theivacumar *et al*., 2007; Darwood *et al*., 2008; Carradice *et al*., 2011) In a

comparative trial, patients returned to normal activities a median of two days after UGFS, compared with 13 days after SVS (Wright *et al*., 2006b).

As mentioned in the Introduction (**Section 1.5.5**), return to work and normal activities can be used as a marker of cost-effectiveness from a societal perspective. A recent study has examined the cost-effectiveness of the available treatments for VV from the perspective of the NHS, (Gohel *et al*., 2010) and found that day-case SVS or EVLA and RFA performed as an outpatient are likely to be cost-effective treatment strategies for patients with primary unilateral GSV reflux, but UGFS despite low initial costs was not cost-effective. This conclusion regarding UGFS was based, however, on only one half of the results of a single RCT (Wright *et al*., 2006b) which found UGFS to be less effective in occluding the GSV than SVS (63% *versus* 86%); however in the same study when the UGFS was administered by sclerotherapists the GSV occlusion rate was 94% at three months. The authors of the cost-effectiveness study state that UGFS would be cost-effective if the probability of GSV occlusion three months after UGFS was the same as that for SVS. (Gohel *et al*., 2010) We have found this to be true; however there are no further published data from an RCT as yet. A large Health Technology Assessment-funded multicentre RCT comparing SVS, EVLA, and UGFS (Comparison of Laser, Surgery and foam Sclerotherapy, CLASS study) is currently recruiting.

In addition, we found UGFS to be a safe procedure. Complications after UGFS can be divided into local (skin necrosis or ulceration, thrombophlebitis and skin pigmentation) and systemic complications (anaphylaxis, DVT and PE, chest symptoms, and neurological symptoms). (Guex, 2009) In our recently published prospective series (1221 procedures in 976 legs including the patients in this study),

we have observed no cases of skin necrosis or ulceration, significant thrombophlebitis in around 5% of cases, and skin pigmentation in around 20% at 1 month which had disappeared in virtually all patients by 12 months. (Bradbury *et al*., 2010) These figures are similar to those found in the literature. (Jia *et al*., 2007)

Anaphylaxis is a recognized complication of liquid sclerotherapy but in a recent systematic review of UGFS no cases of anaphylaxis were found. (Jia *et al*., 2007) There is however a single case report in the literature following UGFS. (Scurr *et al*., 2007) DVT following UGFS remains rare usually occurring in less than 1% of cases as is found in this study. (Jia *et al*., 2007; Myers *et al*., 2007; Gillet *et al*., 2009) One study found that injecting more than 10 ml of foam into a limb resulted in a greater than three-fold increased risk of DVT, (Myers and Jolley, 2008) thus a consensus document now recommends the maximum appropriate amount of foam to be used per session is 10ml. (Breu *et al*., 2008) Hamel-Desnos *et al*. have treated 105 patients with known thrombophilia without a single incidence of DVT or PE. (Hamel-Desnos *et al*., 2009)

Prior to undertaking this research the systemic complications of transient visual disturbance, headache and migraine, and chest symptoms including dry cough had been reported in less than 1% of patients as outlined previously in **Section 1.4.5**. (Guex *et al*., 2005; Jia *et al*., 2007) and this is similar to the findings of the current study. Shortly after the commencement of the studies reported in this Thesis, a case report by Forlee *et al*. on the occurrence of an ischaemic stroke shortly following UGFS led to intense renewed debate regarding the safety of UGFS. (Forlee *et al*., 2006) Following this there have been six other reports of transient neurological events in patients following UGFS, (Hanisch *et al*., 2004; Bush *et al*., 2008; Hartmann

et al., 2009; Hahn *et al*., 2010; Picard *et al*., 2010) although this is not unique to UGFS, with cerebral infarcts also being reported following both SVS and EVLA. (Harzheim *et al*., 2000; Caggiati and Franceschini, 2010) All of the patients were found on investigation to have a patent foramen ovale (PFO). PFO has been previously reported to exist in 26-40% of the general population, (Meier and Lock, 2003; Homma and Sacco, 2005; Rush and Wright, 2008) but more recently this proportion has been shown to be much greater in patients with symptomatic VV. (Raymond-Martimbeau, 2009; Morrison and Neuhardt, 2009; Wright *et al*., 2010) A right-to-left shunt was detected in 59% VV patients in a recent study, although as transcranial Doppler (TCD) was used they were unable to differentiate between intra-cardiac and intra-pulmonary shunts. (Wright *et al*., 2010) Both transthoracic echocardiography and TCD have been used extensively to detect emboli in the heart and middle cerebral artery respectively, and have found that while echogenic signals (foam microemboli) in untreated veins, heart chambers and the cerebral circulation are a common phenomenon during UGFS, neurological complications develop in relatively few patients with right-to-left shunts. (Ceulen *et al*., 2008; Rush and Wright, 2008; Regan *et al*., 2008; Morrison *et al*., 2008, Morrison and Neuhardt, 2009)

Various manoeuvres during foam injection have been suggested to decrease the amount of foam that enters the deep venous system and thus the systemic circulation, thereby improving the safety of UGFS. Leg elevation prior to injection is employed by 69% of surgeons using foam in a survey of the Vascular Society of Great Britain and Ireland, and 63% manually blocked the SFJ or SPJ before injection. (O'Hare and Earnshaw, 2007) In recently published guidelines, leg elevation is recommended but there is no consensus regarding compression at the SFJ or SPJ.

(Breu *et al*., 2008) Hill *et al*. found that the presence of echogenic phenomena in the right heart was significantly higher (100%) in patients injected without leg elevation but with SFJ compression applied, than in patients with their leg elevated and also with SFJ compression (84%). The lowest incidence was in patients injected with their leg elevated but with no SFJ compression (47%). Where SFJ compression was used a concentrated bolus of bubbles was frequently observed after release of digital pressure. (Hill *et al*., 2008) In contrast to this a small study of eight patients suggests that compression (or ligation) of the SFJ may reduce sclerosant foam entering the deep venous system. (Ceulen *et al*., 2010)

Another variation on technique suggested to decrease the passage of foam into the deep veins is the use of multiple small injections rather than larger volumes. (Yamaki *et al*., 2009) However, the small injections were given directly into tributaries prior to direct injections of the saphenous trunk and their occlusion rate of 52% legs at six months was poor. (Yamaki *et al*., 2009)

The final modification of technique is regarding the gas used to generate foam. Most studies have used air, however, there is some evidence that the side-effects are lower using either carbon dioxide or a 70/30 mixture of carbon dioxide and oxygen, (Morrison *et al*., 2008; Morrison *et al*., 2010) however the comparator group was historical and the incidence of side-effects was much higher than those previously reported (8% visual disturbance, 16% cough). The findings are not supported by others. (Cabrera *et al*., 2004; Wright *et al*., 2006b; Ceulen *et al*., 2008)

Further studies are still required to determine the aetiology and significance of these neurological events. While visual disturbance is more common after UGFS, it is also

reported after liquid sclerotherapy suggesting that the mechanism cannot simply be related to bubbles persisting in the systemic circulation, but could be due to vasospasm induced by the sclerosant itself. (Guex *et al*., 2005; Hamel-Desnos and Allaert, 2009; Bradbury *et al*., 2010; O'Hare *et al*., 2010) There is further evidence that the visual disturbances correspond with migraine with aura, thus suggesting that they are not transient ichaemic events but possibly due to endothelin release from the damaged vein. (Gillet *et al*., 2010)

In the UK, after two separate comprehensive reviews of the evidence, UGFS has been accepted as a safe treatment by the National Institute of Health and Clinical Excellence (NICE), and by the major private insurance companies and the majority of vascular surgeons. (Bradbury *et al*., 2010)

A weakness of the study is that the two groups were not randomized. Two surgeons in our unit used UGFS as the preferred treatment for VV, whereas other colleagues continued to employ conventional SVS. All patients in the present study were referred from general practitioners through a common UK NHS referral pool. The hospital management system allocated patients to each vascular surgeon in accordance to their capacity to offer treatment. Therefore, there was little or no clinical or surgeon selection bias, which explains why, despite the lack of formal randomization, the UGFS and SVS groups were so similar.

Another limitation of the present study was the discrepancy in size of the UGFS and SVS cohorts, although this was unlikely to have resulted in any systematic bias. Assessment of severity of bruising and pain were subjective, and decided by the patient. This could have been improved by objective assessment of bruising in a

follow-up clinic, and by using a validated pain score, but arguably the patient's assessment of his or her post-operative recovery remains the most important outcome measure.

In conclusion, this questionnaire study showed that, when compared with SVS, UGFS was associated with significantly less pain, bruising and analgesia use, and time off work and driving. The low incidence of complications in the UGFS group gives further evidence of its safety.

CHAPTER 4. PATIENT-REPORTED OUTCOMES FOLLOWING ULTRASOUND-GUIDED FOAM SCLEROTHERAPY

Extended outcome measures, including patient-reported outcomes, are useful for measuring the success of any intervention for VV particularly when the clinical efficacy is similar. These outcomes give health providers more information about the patient's experience of the disease and the effectiveness of any intervention.

In this Chapter I will be looking at measures of functional status (HRQL) and also patient satisfaction by examining the patient's expectations of treatment, and whether these expectations are met.

4.1 Changes in health-related quality of life following ultrasound-guided foam sclerotherapy for great and small saphenous varicose veins

The data contained within this Chapter were

- presented at the International Surgical Congress of the Association of Surgeons of Great Britain and Ireland in Glasgow, UK in May 2009
- published in the Journal of Vascular Surgery in April 2010 (Darvall *et al*., 2010b).

4.1.1 Introduction

Measuring HRQL is a comprehensive way to assess the effect of VV on patients, and whether surgical interventions produce improvement. (Smith *et al*., 1999) Valuable information is gained on the patient-perceived burden of illness. The use of both generic and disease-specific measures is important when HRQL is assessed, and a variety of venous disease-specific measures have been developed and validated.

CVD, including VV and CVU, is associated with a reduced HRQL. (Smith *et al*., 1999; Kaplan *et al*., 2003; Sam *et al*., 2004a; Kahn *et al*., 2004) Both disease-specific and generic HRQL improve following SVS for VV, (Baker *et al*., 1995; Smith *et al*., 1999; Durkin *et al*., 2001; MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam 2004b, Subramonia and Lees, 2005) and this is also the case with EVLA and RFA. (Rautio *et al*., 2002; Lurie *et al*., 2003) The effects of UGFS on HRQL are unknown.

The aim of this study, therefore, is to determine the effect of UGFS for VV on both generic and disease-specific HRQL.

4.1.2 Methods

4.1.2.1 Patients and follow-up

Following local ethical committee approval and obtaining written informed consent, consecutive patients undergoing UGFS between April 2005 and May 2007 were invited to take part in the study (as per **Section 2.1.2.1)**.

To be considered suitable for UGFS patients had to have symptomatic, CEAP C_{2-6} venous disease (i.e. treatment was not offered for cosmetic indications) and significant (>0.5s) reflux in the GSV or SSV.

HRQL questionnaires were posted to all patients one week prior to treatment, and at one, six and 12 months after treatment. If patients were having bilateral treatments these were done at least four weeks apart, and the questionnaires were completed one, six and 12 months after the first treatment to the first leg. No reminders were sent. Patients who did not bring the completed questionnaires with them to their first treatment session were excluded from the study.

4.1.2.2 HRQL questionnaires

The HRQL questionnaires were a generic measure, the SF12 (**Appendix 1**) and a disease-specific measure, the AVSS (**Appendix 2**).

The SF12 consists of 12 questions about general health and provides two summary scores, the PCS which represents physical functioning, and the MCS which represents mental functioning. The mean PCS and MCS of the general population is 50 with a standard deviation of 10: the higher the score, the better the HRQL.

The AVSS comprises 13 questions about leg symptoms and provides a final score between 0 and 100; a higher score denotes a poorer disease-specific HRQL.

4.1.2.3 UGFS treatment

UGFS treatment was performed as described in **Section 2.1.2.3**.

4.1.2.4 Statistical analysis

SPSS version 17.0 was used for data analysis. Mann-Whitney *U* test (MWU, for numerical variables) and X^2 test (categorical variables) were used as appropriate to determine any significant differences between responders and non-responders at each time-point. Wilcoxon signed ranks test (WSR) was used to assess the intra-group change in PCS, MCS and AVSS following treatment, and MWU test was used to determine inter-group differences in HRQL scores between sub-groups.

4.1.3 Results

4.1.3.1 Patients

Questionnaires were sent to 351 consecutive patients between April 2005 and May 2007, and 296 (84.3%) returned questionnaires and agreed to enrol in the study. **Table 4.1** summarizes the baseline characteristics for each patient. Treatment was to the GSV alone in 221 patients (74.7%), to the SSV alone in 30 (10.1%), and to both the GSV and SSV in 45 (15.2%). Deep and superficial reflux was combined in 12 patients. A second treatment was required in 72 legs (18%) before 12 months; two of these had three treatment sessions.

Table 4.1 Demographic data of responders

	Pre-treatment responders	1 month responders	6 month responders	12 month responders
No. of patients	296	242	216	204
Age: in years†	57 (45-67)	57 (46-67)	60 (49-69)	59 (48-69)
Sex: male‡	102 (34)	82 (34)	76 (35)	66 (32)
Recurrent disease‡	72 (24)	54 (22)	45 (21)	45 (22)
Bilateral disease‡	99 (33)	79 (33)	69 (32)	69 (34)
Pre-treatment: CEAP C_{4-6}, worst leg‡	102 (34)	74 (32)	77 (36)	68 (33)
PCS†		47.1 (39.9-53.2)	46.5 (38.2-52.6)	47.0 (39.9-53.1)
MCS†		52.6 (43.5-57.3)	52.4 (42.3-57.5)	53.6 (44.8-57.9)
AVSS†		19.0 (12.7-26.2)	19.6 (12.7-27.1)	18.5 (12.6-25.7)

Values in table are median (IQR)† or number (percentage)‡

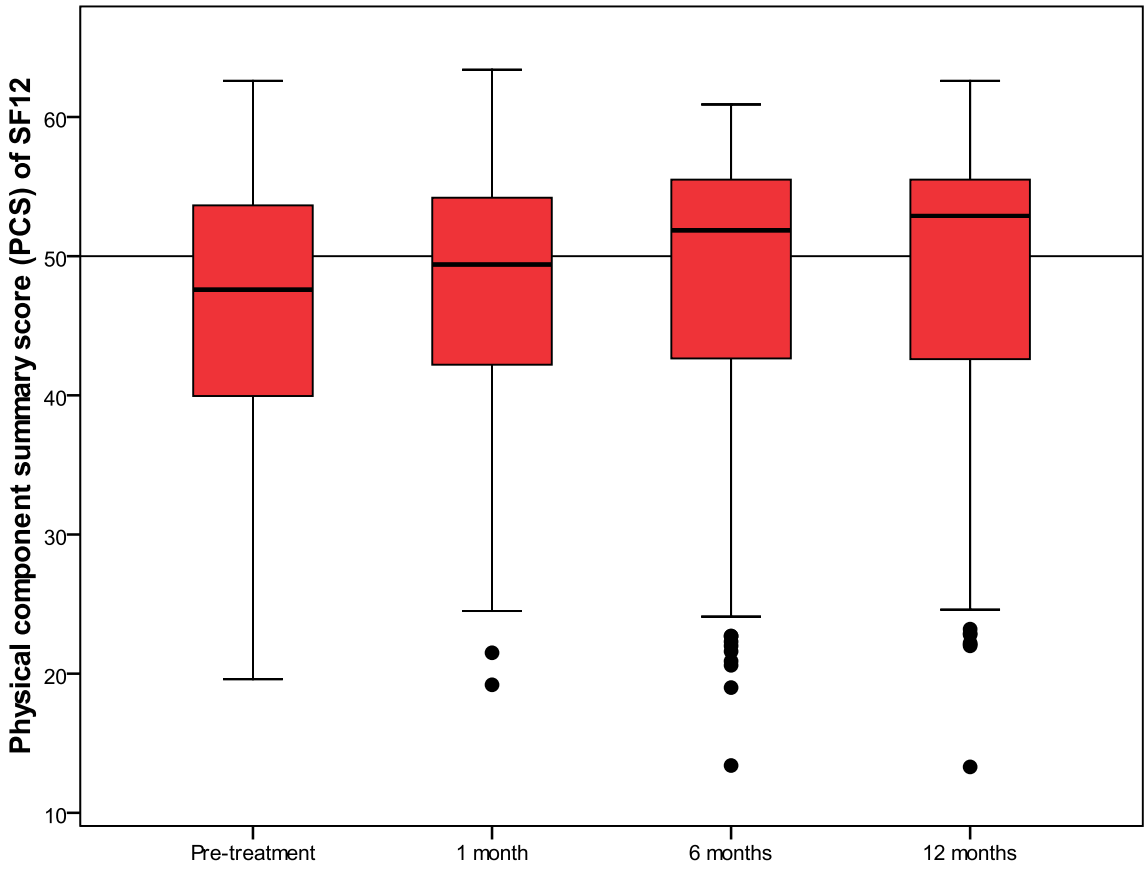
Of the 296 patients entered into the study, 242 returned questionnaires at one month (81.8%), 216 at six months (73.0%) and 204 at 12 months (68.9%). There were no significant differences between responders and non-responders both pre-treatment and at one month in terms of age, gender, previous SVS, bilateral disease and CEAP clinical grade. (**Table 4.1**) Patients who returned questionnaires six and 12 months after treatment were significantly older than non-responders with a median difference of 13 years at six months (P < .0005, MWU), and a median difference of seven years at 12 months (P < .0005, MWU).

Pre-treatment median PCS was significantly worse (lower) in responders than non-responders at six months (46.5 *versus* 48.4, P = .017, MWU); pre-treatment median MCS was significantly better (higher) in responders at 12 months (53.6 *versus* 49.8, P = .010, MWU). No other differences in pre-treatment scores between responders and non-responders were documented at each evaluation.

4.1.3.2 Physical component summary score of SF12 (PCS)

The PCS significantly improved during the first month after treatment, from a median at baseline of 47.6 to 49.4 (P = .008; WSR), and continued to 51.9 (P < .0005) at six months and to 52.9 (P < .0005) at 12 months (**Figure 4.1**). Further significant improvement was also seen between both one and six months (49.4 *versus* 51.9, P < .0005), and six and 12 months (51.9 *versus* 52.9, P < .0005) (**Figure 4.1**).

Figure 4.1 Box and whisker plot indicating SF12 PCS before and at 1, 6 and 12 months after UGFS

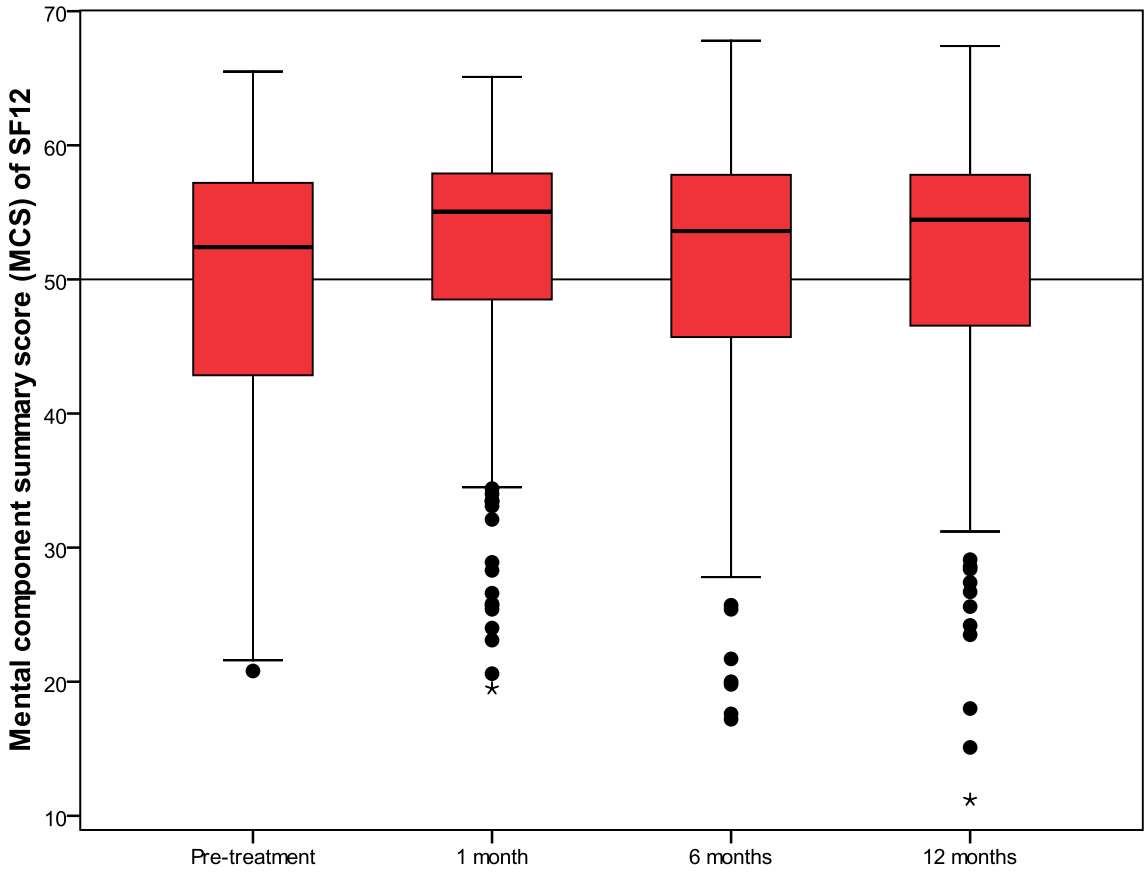


The horizontal line inside each box indicates the median; the box itself represents the IQR. Dots represent outliers which are observations lying more than 1.5 times the IQR from the first or third quartile. Asterisks represent extremes which are values more than 3 times the IQR above or below the third or first quartile respectively. Whiskers represent the largest and smallest values that are not outliers or extremes. The reference line is set at 50, the general population mean.

4.1.3.3 Mental component summary score of SF12 (MCS)

There was a significant improvement in MCS during the first month after treatment, from a median of 52.4 to 55.1 (P < .0005; WSR), but this was not sustained at six and 12 months post-treatment (**Figure 4.2**).

Figure 4.2 Box and whisker plot indicating SF12 MCS before and at 1, 6 and 12 months after UGFS

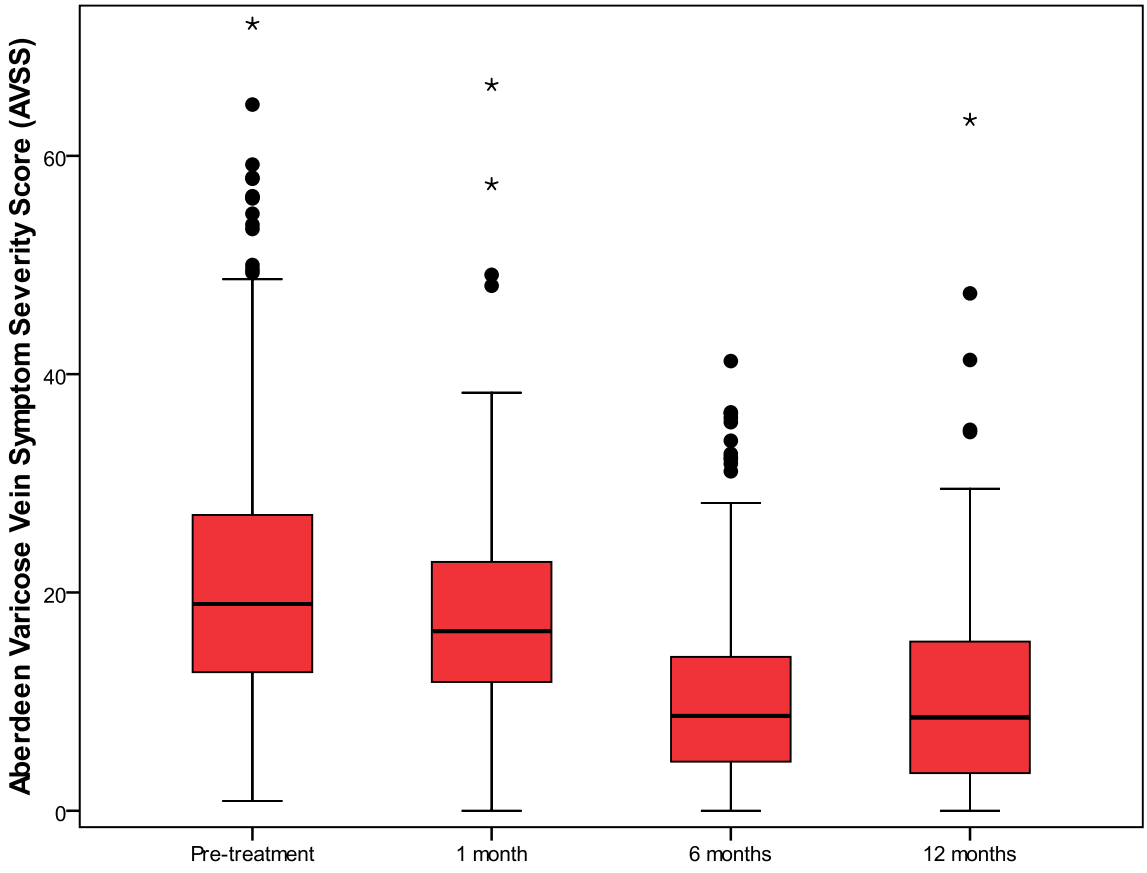


4.1.3.4 Aberdeen Varicose Vein Symptom Severity Score (AVSS)

AVSS significantly improved after treatment from a median baseline of 19 to 16.5 at one month (P < .0005), which continued to improve to 8.7 at 6 months (P < .0005) and to 8.6 at 12 months (P < .0005) (**Figure 4.3**).

There was also further significant improvement seen between one and six months (16.5 *versus* 8.7, P < .0005), but not after six months (8.7 *versus* 8.6, P = .702) (**Figure 4.3**).

Figure 4.3 Box and whisker plot indicating AVSS before and at 1, 6 and 12 months after UGFS



4.1.3.6 Subgroup analyses

There were no differences in PCS, MCS or AVSS according to whether the treated vein was GSV alone or SSV alone, and no differences in PCS or MCS according to whether the treated veins were primary or recurrent.

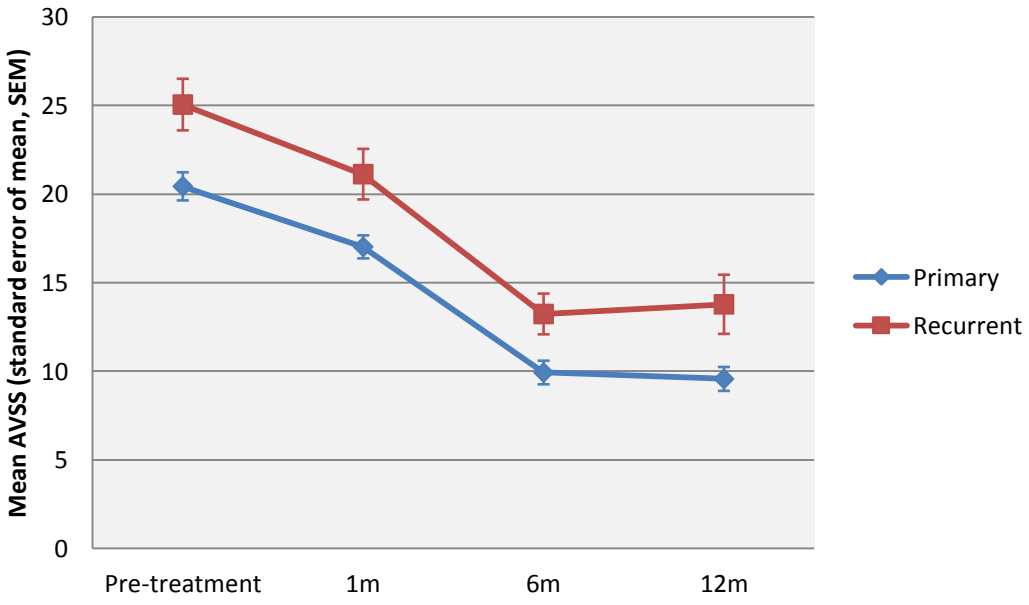
AVSS was significantly higher (worse) at all measured intervals in patients treated for recurrent VV (**Table 4.2, Figure 4.4**). Both groups of patients showed similar improvement during the 12 months after treatment (**Table 4.2, Figure 4.4**).

Table 4.2 Changes in AVSS after UGFS in patients with primary and recurrent VV

	Primary	Recurrent	P†
AVSS			
Pre-treatment	18.0 (12.3-25.2)	23.3 (16.6 -30.4)	.001
1 month	16.0 (11.0-21.8)	20.2 (13.1-26.5)	.006
6 months	7.5 (3.4-14.2)	12.0 (6.9-16.2)	.002
12 months	8.2 (2.4-14.6)	12.3 (6.4-20.2)	.005
Change in AVSS‡			
0-1 month	P<.0005	P=.109	
0-6 months	P<.0005	P<.0005	
0-12 months	P<.0005	P<.0005	

Values are median (IQR); † = P value from MWU test; ‡ = P values from WSR test

Figure 4.4 Changes in AVSS after UGFS in patients with primary and recurrent VV



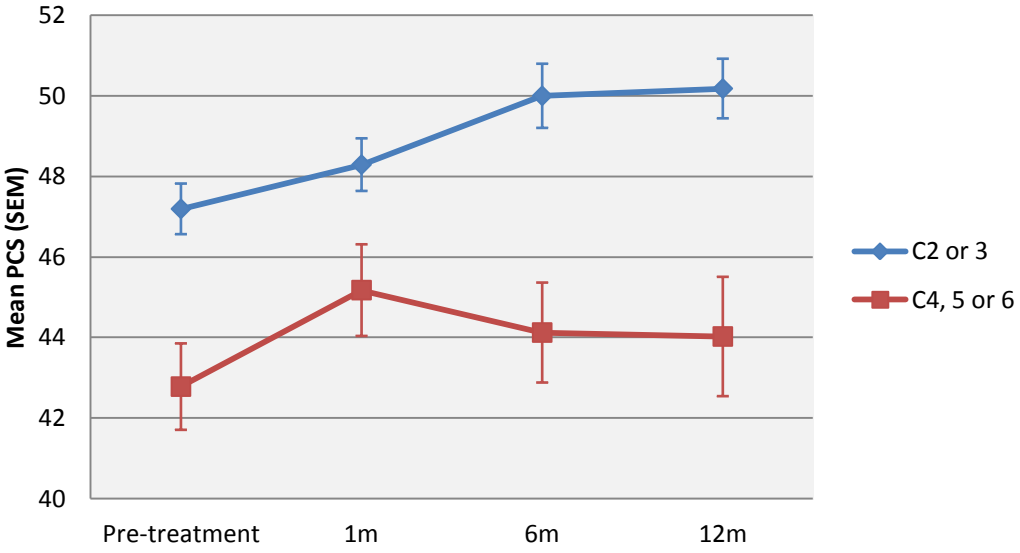
There was no difference in MCS according to whether the treated veins were uncomplicated (CEAP C_{2-3}) or complicated (CEAP C_{4-6}). PCS was significantly lower (worse) at all measured intervals in patients treated for complicated VV (**Table 4.3, Figure 4.5**). PCS improved significantly during the 12 months after treatment in both uncomplicated and complicated VV compared with pre-treatment values (**Table 4.3, Figure 4.5**). The improvement in PCS was greater in those with uncomplicated VV.

Table 4.3 Changes in SF12 PCS after UGFS in patients with uncomplicated (CEAP C_{2-3}) and complicated (CEAP C_{4-6}) VV

	Uncomplicated C2-3	Complicated C4-6	P†
PCS			
Pre-treatment	49.1 (41.6-53.9)	45.0 (32.9-51.5)	.001
1 month	50.1 (43.8-55.3)	47.6 (38.0-52.8)	.022
6 months	53.9 45.8-55.9)	45.9 (36.1-53.5)	<.0005
12 months	53.7 (46.4-55.9)	47.3 (34.3-54.8)	<.0005
Change in PCS‡			
0-1 month	P=.085	P=.044	
0-6 months	P<.0005	P=.014	
0-12 months	P<.0005	P=.327	

Values are median (IQR); † = P value from MWU test; ‡ = P values from WSR test

Figure 4.5 Changes in SF12 PCS after UGFS in patients with uncomplicated (CEAP C_{2-3}) and complicated (CEAP C_{4-6}) VV



AVSS was significantly higher (worse) at all measured intervals in patients treated for complicated VV (**Table 4.4, Figure 4.6**). Both groups of patients showed similar improvement during the 12 months after treatment (**Table 4.4, Figure 4.6**).

4.1.4 Discussion

The main finding of the current study is that significant improvements in both generic and disease-specific HRQL are seen after UGFS for VV, and are sustained to at least 12 months.

Despite previously held beliefs that VV are simply a cosmetic issue for most patients, several studies have shown poorer generic HRQL (particularly in physical domains) in patients with CVD compared with the general population. (Sam *et al*., 2004a; Kahn *et al*., 2004) Indeed, SF36 PCS scores in patients with healed or active CVU are

similar to those previously reported for patients with chronic obstructive pulmonary disease, osteoarthritis or angina. (Kahn *et al*., 2004)

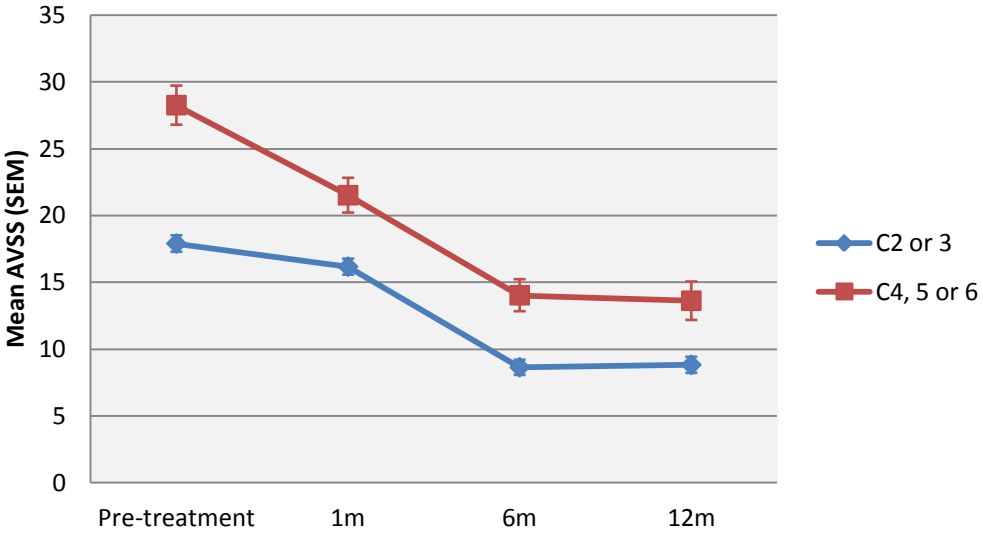
When outcomes of treatment are assessed, it is important to consider change in HRQL with disease-specific as well as generic measures. Generic HRQL measures allow the NHS to compare interventions to enable appropriate allocation of resources. Disease-specific measures for VV are useful for demonstrating non-inferiority of the newer minimally invasive techniques compared with traditional SVS.

Table 4.4 Changes in AVSS after UGFS in patients with uncomplicated (CEAP C_{2-3}) and complicated (CEAP C_{4-6}) VV

	Uncomplicated C2-3	Complicated C4-6	P†
AVSS			
Pre-treatment	17.3 (12.0-22.6)	26.6 (17.5-35.8)	<.0005
1 month	15.8 (10.9-21.0)	18.5 (13.7-27.6)	<.0005
6 months	7.3 (4.0-12.6)	11.5 (5.4-20.4)	<.0005
12 months	7.7 (3.3-13.3)	12.6 (5.0-18.8)	.006
Change in AVSS‡			
0-1 month	P=.068	P<.0005	
0-6 months	P<.0005	P<.0005	
0-12 months	P<.0005	P<.0005	

Values are median (IQR); † = P value from MWU test; ‡ = P values from WSR test

Figure 4.6 Changes in AVSS after UGFS in patients with uncomplicated (CEAP C_{2-3}) and complicated (CEAP C_{4-6}) VV



The SF36 from the Medical Outcomes Survey is the generic HRQL measure most often used to demonstrate improvement after conventional SVS. Several groups have examined changes in SF36 scores after SVS with follow-up durations from one week to two years. Physical functioning generally worsened in the first month after SVS, (Baker *et al*., 1995; Chetter *et al*., 2006; Rasmussen *et al*., 2007) but had improved to better than pre-treatment values by six weeks to three months. (Smith *et al*., 1999; Chetter *et al*., 2006; Rasmussen *et al*., 2007) Other studies found that this improvement was sustained to at least one year after SVS, (Durkin *et al*., 2001; Michaels *et al*., 2006, Blomgren *et al*., 2006) and a previous report from our group found a significant improvement in pain, physical functioning and SF36-PCS at two years after SVS. (Sam *et al*., 2004a) Three of the studies used an additional measure of generic HRQL, the EuroQol, and this too found improved HRQL at six weeks to one year after SVS. (Durkin *et al*., 2001; Michaels *et al*., 2006; Chetter *et al*., 2006) Most improvement seen was in physical domains, but mental health also improved

one month after SVS in two studies, (Smith *et al*., 1999; Chetter *et al*., 2006) although no change was seen in mental health in the studies with longer follow-up. This is similar to the findings of the current study where physical functioning (PCS) showed sustained improvement as early as one month after UGFS, whereas mental health (MCS) showed an early, but short-lived, improvement. RCTs comparing improvement in generic HRQL after EVLA and SVS, found similar improvements in the physical domains of SF36 between three months and two years after treatment. (Rasmussen *et al*., 2007; Christenson *et al*., 2010; Rasmussen *et al*., 2010; Carradice *et al*., 2011) Only Carradice *et al*. looked at HRQL one week post-treatment and found that patients undergoing EVLA had significantly less deterioration in generic physical HRQL after one week than those undergoing SVS. (Carradice *et al*., 2011)

The SF12 is a fully-validated adaptation of the SF36 that is quicker to complete and has been shown to give results comparable to those of the SF36. (Jenkinson *et al*., 1997; Hurst *et al*., 1998; Ware *et al*., 2002) Our group has previously looked at improvement in SF12 after SVS and found, as expected, similar significant improvements in physical HRQL at three, six and 12 months, but no improvement in mental HRQL. (Sam *et al*., 2004a; Sam *et al*., 2006) Shepherd *et al.* used the SF12 in their RCT comparing EVLA and RFA and found similar improvements six weeks after treatment. (Shepherd *et al*., 2010a)

The AVSS has been the most widely used disease-specific measure in assessing VV treatment, including conventional SVS and EVLA. AVSS appears to worsen slightly one to two weeks after SVS before reaching pre-treatment levels or, more commonly, improving by four to six weeks. (Smith *et al*., 1999; MacKenzie *et al*.,

2002a; MacKenzie *et al*., 2002b; Subramonia and Lees, 2005; Chetter *et al*., 2006; Rasmussen *et al*., 2007) Similar results were also found after EVLA and RFA, (Theivacumar *et al*., 2007; Darwood *et al*., 2008; Theivacumar *et al*., 2008; Carradice *et al*., 2009; Shepherd *et al*., 2010a; Subramonia and Lees, 2010) with one RCT documenting no difference in the improvement seen between EVLA or conventional SVS out to three months. (Rasmussen *et al*., 2007) One study compared SVS (SFJ ligation, stripping of the GSV, and multiple stab avulsions) with a combination of SVS (SFJ ligation alone) and UGFS. (Bountouroglou *et al*., 2006) Both groups showed similar improvement in AVSS with three months follow-up. In studies that have looked at improvement beyond three months, an RCT by Darwood *et al.* found similar sustained improvement in AVSS in SVS and EVLA groups at one year, (Darwood *et al*., 2008) and our group found sustained improvement in AVSS at 2 years after SVS. (MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002)

Two studies used the Chronic Venous Insufficiency Questionnaire (CIVIQ), an alternative validated disease-specific HRQL measure, (Launois *et al*., 1996) to assess change after treatment. One multicentre RCT compared CIVIQ scores at three months after sclerotherapy with either 3% polidocanol foam or 3% polidocanol liquid. (Rabe *et al*., 2008) Patients in both treatment groups improved, but improvement was greater in the foam group. The other study, also an RCT, compared CIVIQ scores out to four months after SVS or RFA, and found similar improvements at four months, but a quicker improvement in HRQL, in the RFA group. (Lurie *et al*., 2003)

The current study provides further evidence that VV treatment results in significantly improved generic and disease-specific HRQL. In particular, to our knowledge, this is

the first study of its kind to look specifically at UGFS, and thus allows UGFS to be compared with other treatments for VV and also interventions available for other conditions to aid allocation of healthcare resources. The other studies looking at HRQL after UGFS are limited because of short follow-up, by the use of only a disease-specific instrument, (Rabe *et al*., 2008) by looking at a combination of SVS and UGFS, (Bountouroglou *et al*., 2006) or by simply asking patients whether their quality of life had improved. (Barrett *et al*., 2004)

Our previous studies have shown that recurrent VV are more symptomatic at baseline than primary VV, and that the improvement in HRQL (measured by AVSS) after SVS for recurrent VV is less than that achieved for primary disease. (MacKenzie *et al*., 2002b) The results from the current study after UGFS were very similar. The degree of improvement in AVSS after UGFS for recurrent VV paralleled that for primary VV, yet the HRQL was significantly worse in the recurrent VV group at all follow-up intervals. One advantage of UGFS is that it is easy to treat recurrent VV when compared with redo SVS.

As expected, AVSS in patients with complicated VV (CEAP C_{4-6}) was worse at each follow-up interval than in those with uncomplicated VV (CEAP C_{2-3}), as previously found in SVS patients. (MacKenzie *et al*., 2002b) Interestingly, the patients with uncomplicated VV had a much greater improvement in PCS during the 12 months after UGFS than those with complicated VV, suggesting that even though uncomplicated VV are considered a relatively minor problem, patients have as much, if not more, to gain from treatment than complicated VV. Indeed, two recent trials have shown that SVS for uncomplicated VV provides significant benefit over conservative treatment in terms of health status, HRQL and patient satisfaction at a

relatively small cost, (Michaels *et al*., 2006; Ratcliffe *et al*., 2006) yet rationing of treatment for uncomplicated symptomatic VV remains widespread. (Nasr *et al*., 2008)

A limitation of the current study is the number of questionnaires available for follow-up analysis. A 69% response rate at 12 months is not as good as we had hoped but is comparable with other questionnaire studies, and better than many involving VV patients. The response rate could likely have been improved if reminders had been sent to non-responders, or if the questionnaires were administered in a face-to-face interview, but this would have introduced interviewer bias. The initial sample size was also large enough that the power of the study was not compromised.

Another limitation is the lack of a control group. We do not apologise for this as this is an observational study of our practice, and according to our experience in the last few years, over 90% of our patients prefer to have UGFS and would therefore not consent to be randomised to SVS or UGFS. In addition, we have already published HRQL results after conventional SVS. (MacKenzie *et al*., 2002a; MacKenzie *et al*., 2002b; Sam *et al*., 2004a; Sam *et al*., 2006)

Further study is of course required to ascertain the longevity of the HRQL improvement seen after UGFS, and indeed after EVLA and RFA, and we are continuing follow-up of our cohort.

In conclusion, significant improvements are seen in both generic and disease-specific HRQL following UGFS and this is sustained to at least 12 months after treatment.

4.2 Patients' expectations before and satisfaction after ultrasound guided foam sclerotherapy for varicose veins

The data contained within this Chapter were

- presented at the International Surgical Congress of the Association of Surgeons of Great Britain and Ireland in Glasgow, UK in May 2009
- published in the European Journal of Vascular and Endovascular Surgery in November 2009 (Darvall *et al*., 2009d).

4.2.1 Introduction

Up to 20% of patients have reported dissatisfaction with SVS and such surgery remains the commonest cause of litigation against vascular surgeons in the UK. (Davies *et al*., 1995; Ray, 2005; Scurr and Scurr, 2005) It has been suggested that this is due to unrealistic expectations of surgery. (Davies *et al*., 1995; MacKenzie *et al*., 2002b; Ray, 2005; Scurr and Scurr, 2005) However, unless one knows what those expectations are and understands the limitations of the treatments one is offering, one cannot define what is unrealistic and what is not. When specifically asked, most patients admit to having a wide variety of expectations in relation to their VV treatment, many of them probably unanticipated by the clinician. It is perhaps not surprising, therefore, that the patient and the clinician can find themselves inadvertently talking at cross-purposes with resulting dissatisfaction and even recourse to medico-legal action. (Ray, 2005)

The aim of this study, therefore, is to examine patients' expectations before and satisfaction after UGFS for VV in terms of relief of lower limb symptoms, improvement in appearance, and beneficial effect on lifestyle.

4.2.2 Methods

4.2.2.1 Patients

Following local ethical committee approval and obtaining written informed consent, consecutive patients undergoing UGFS for symptomatic VV between April 2005 and May 2007 were invited to take part in the study (as per **Section 2.1.2.1**).

Questionnaires were sent to 351 patients (464 treated legs) one week prior to (**Appendix 5**) and six months after (**Appendix 6**) treatment.

To be considered suitable for UGFS patients had to have symptomatic, CEAP C_{2-6} venous disease (i.e. treatment was not offered for cosmetic indications) and significant (>0.5s) reflux in the GSV or SSV on DUS.

4.2.2.2 Pre-treatment assessment

Patients were examined and the severity of venous disease according to the CEAP clinical classification was determined (**Table 1.1**).

DUS was performed, as described in **Section 2.1.2.2**, at the initial clinic attendance in order to identify sites of superficial, deep and communicating venous reflux.

4.2.2.3 UGFS treatment

UGFS treatment was performed as described in **Section 2.1.2.3**.

4.2.2.4 Pre-treatment questionnaire

Section 1 asked how much improvement was expected in lower limb symptoms (pain or aching, itching, tingling, cramps, restless legs, swelling and heaviness). The answers were sought separately for each leg to be treated. Section 2 asked about expected improvements in appearance, life-style (choice of clothes, work performance, social and leisure activities) and relationships. Possible responses were ‘an awful lot’, ‘a lot’, ‘quite a bit’, ‘a little’, and ‘not at all’ or ‘I do not have this symptom’.

4.2.2.5 Post-treatment questionnaire

Patients were asked to grade the improvement (if any) that they had experienced in terms of symptoms, appearance, life-style and relationship using the same menu of responses. Pre- and post-treatment questionnaires were compared to ascertain whether expectations had been met.

4.2.2.6 Analysis

The responses ‘an awful lot’ and ‘a lot’ were grouped together to represent ‘a significant improvement’, and the responses ‘quite a bit’ and ‘a little’ were combined to signify ‘a moderate improvement’.

Symptoms were analysed by the number of limbs treated; other outcomes by number of patients. Subgroup analysis was performed to determine the effects of age, gender, CEAP clinical grade, and previous SVS on the expectations and whether they were met using Chi-squared (χ^2). SPSS version 17.0 was used for data analysis.

4.2.3 Results

4.2.3.1 Patient characteristics and response rates

The pre-treatment questionnaire was returned by 282 (80.3%) patients, and 281 (80.1%) returned the post-treatment questionnaire (**Table 4.5**); 209 patients (59.5%) completed both questionnaires. Patients who completed post-treatment questionnaires (median age 59 years, IQR 48-68 years for responders; median 49 years, IQR 39-61 years for non-responders; P < .0005, MWU) and those who returned both questionnaires (median age 60 years, IQR 50-69 years for responders; median age 51 years, IQR 40-62 years for non-responders; P < .0005, MWU) were significantly older than the non-responders. Otherwise, there were no significant differences between responders and non-responders including gender, CEAP clinical grade, and the proportion being treated for recurrent disease after previous SVS

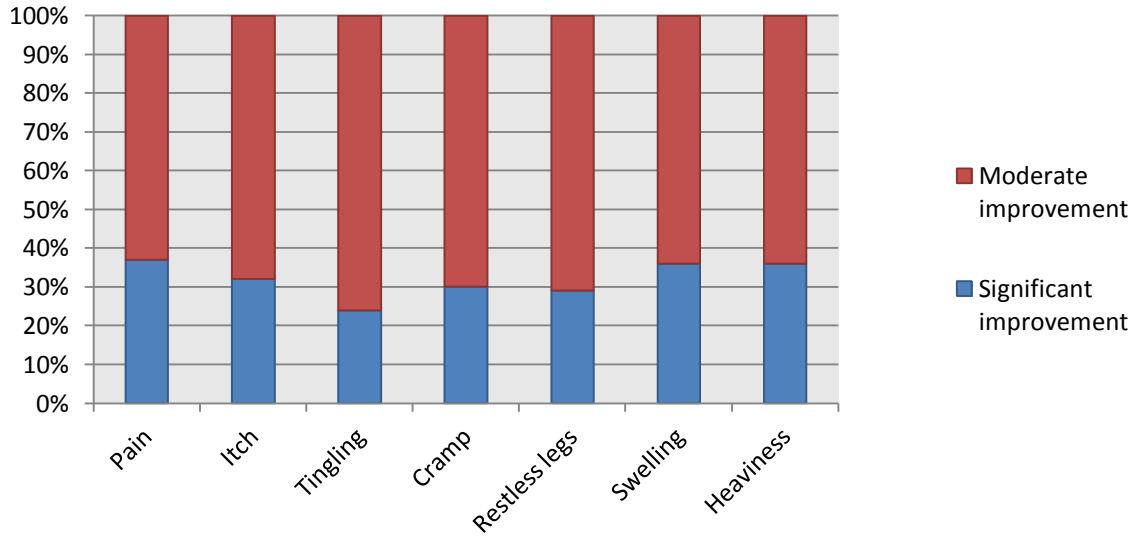
.

Table 4.5 Demographic data of responders

	Pre-treatment responders	Post-treatment responders
No. of patients	282	281
No. of legs	373	365
Age: median (IQR) in years	57 (45-67)	60 (50-69)
Male sex[†]	100 (35.5)	99 (35.2)
Bilateral[†]	91 (32.3)	84 (29.9)
Recurrent[‡]	107 (28.7)	96 (26.3)
CEAP C_2 or C_3[‡]	249 (66.8)	258 (70.7)

Values in parentheses are percentages of patients[†] or legs[‡]

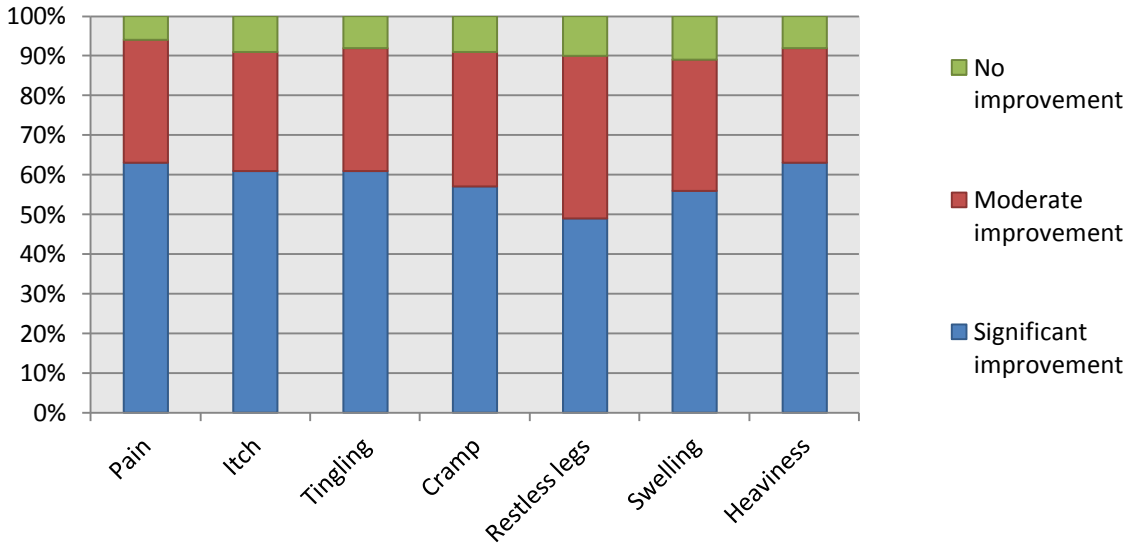
Figure 4.7 Percentage of limbs in which a significant or moderate improvement in each lower limb symptom was expected prior to treatment



4.2.3.2 Lower limb symptoms

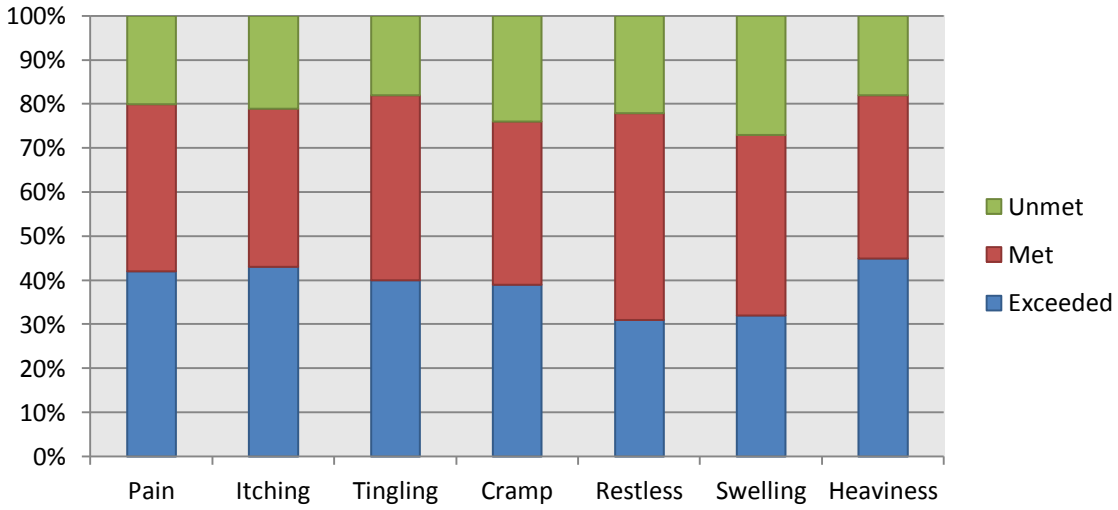
These data were analysed by leg. Pre-treatment questionnaires were returned for 373 legs (80.4%), post-treatment questionnaires for 365 legs (78.7%), and both questionnaires for 270 legs (58.2%). Pain or ache was the most common symptom being present in 84.7% of legs. Itching, restlessness, swelling, heaviness and cramp were less common occurring in 70.2%, 64.6%, 64.1%, 60.9% and 55.2% of the legs respectively; and tingling was the least common symptom occurring in only 37.5% of legs. A significant improvement in symptoms was expected in around one-third of legs, and a moderate improvement in the remaining two-thirds (**Figure 4.7**). Between 48.8% and 63.2% of legs had a significant improvement in symptoms after UGFS, around 10% showed no improvement at all (**Figure 4.8**).

Figure 4.8 Percentage of limbs with improvement in lower limb symptoms six months following treatment



Expectations in respect of lower limb symptoms were met or exceeded in around 80% of legs (**Figure 4.9**).

Figure 4.9 Percentage of limbs in which expectations of improvement in each lower limb symptom were exceeded, met or unmet

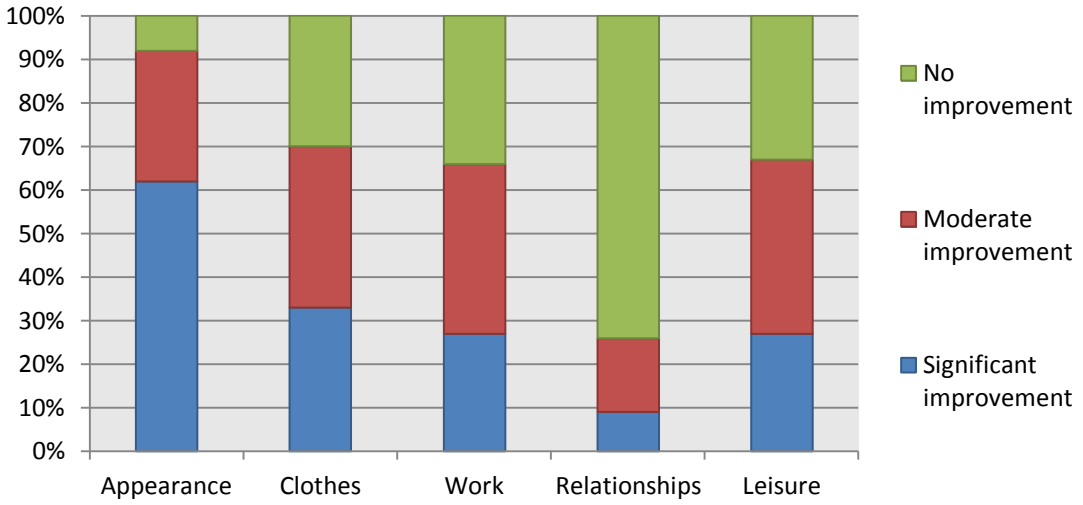


Patients who had had previous SVS were less likely to have their expectations met than those with primary veins in terms of pain (71% *versus* 83.3%, P = .042), tingling (58% *versus* 91%, P = .002), and restless legs (66% *versus* 83%, P = .033).

4.2.3.3 Appearance

These data are analysed by patient. Over 90% of patients expected an improvement in the appearance of their legs (**Figure 4.10**); 96.1% of patients experienced a significant cosmetic improvement (**Figure 4.11**); and 85.6% of patients had their pre-intervention cosmetic expectations met (**Figure 4.12**).

Figure 4.10 Percentage of patients expecting an improvement in appearance, and social and leisure activities prior to treatment



4.2.3.4 Life-style benefits

Approximately two-thirds of patients expected to be able to wear different clothes as well as an improvement in their working performance and social and leisure activities clothes as a result of their treatment (**Figure 4.10**). Over 50% of patients experienced such improvements (**Figure 4.11**) and almost 75% of patients had their expectations met with regard to these outcomes (**Figure 4.12**).

4.2.3.5 Relationships

One quarter of patients expected improvement in their personal relationships following treatment (**Figure 4.10**) and about 30% experienced such an improvement

(**Figure 4.11**). However, over 80% who had hoped for such an improvement had their expectations met or in a quarter of cases exceeded (**Figure 4.12**).

Figure 4.11 Percentage of patients who had an improvement in appearance, and social and leisure activities six months after treatment

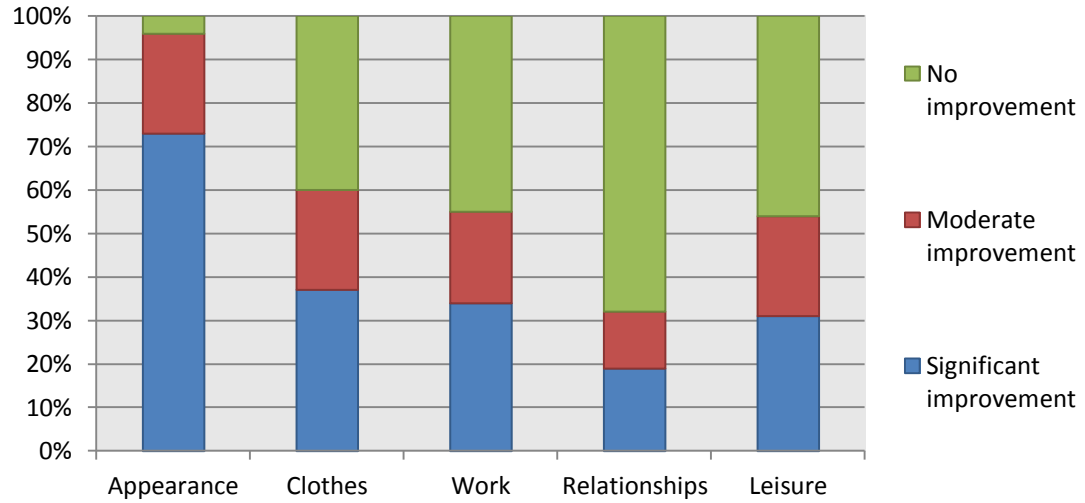
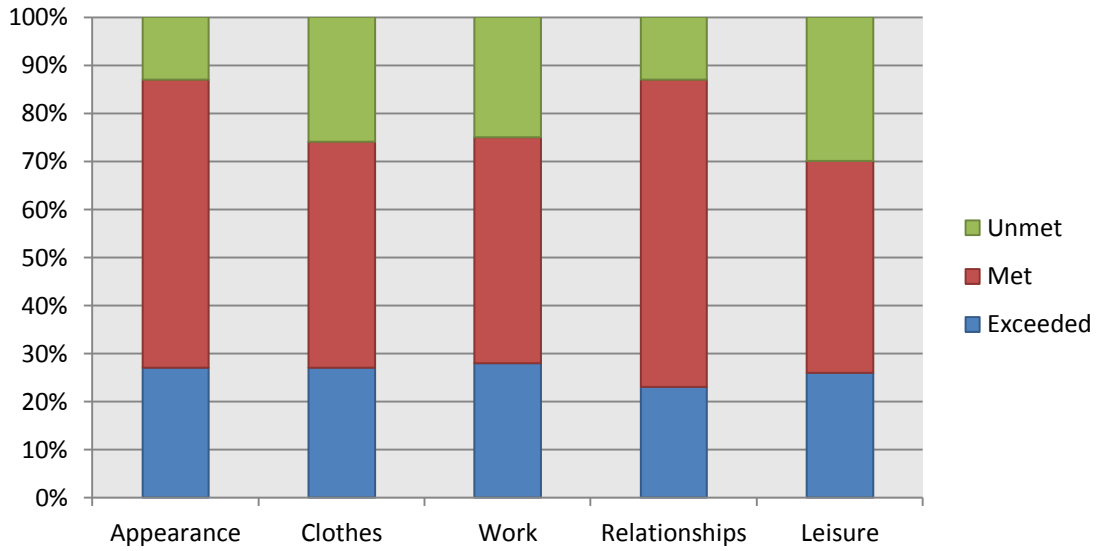


Figure 4.12 Percentage of patients in whom the expected improvements in appearance, social and leisure outcomes were exceeded, met or unmet



4.2.3.6 Factors affecting outcomes

There was no difference in terms of cosmetic and social expectations according to whether the patient had had previous SVS or not. Younger patients (<55 *versus* ≥55 yrs) were significantly more likely to be expecting an improvement in appearance of their legs (96.0% *versus* 89.2%, P = .034), and the same was true for C_2 disease compared with $C_{5/6}$ (97.5% *versus* 68%, P < .0001). Women (80.8% *versus* 49.0%, P < .0001), patients <55 yrs (77.6% *versus* 64.3%, P = .016) and C_2 patients (*versus* $C_{5/6}$; 77.5% *versus* 46%, P = .0001) were all more likely to expect improvements in their ability to wear different clothes after treatment. There were no observed differences in expectations of improvement in terms of work, relationships and social and leisure activities by gender, age, previous SVS or CEAP clinical grade.

4.2.4 Discussion

The main finding of this study is that UGFS for VV produces significant improvements in lower limb symptoms, cosmetic appearance, life-style and relationships in the majority of patients. Furthermore, the great majority who expect such benefits have their expectations met or exceeded.

Virtually all patients were expecting treatment to improve their lower limb symptoms, and most did report such an improvement and had their expectations met or exceeded. In this regard, UGFS appears to be at least as effective as SVS, (Davies *et al*., 1995; Campbell *et al*., 2003; Barrett *et al*., 2004; Michaels *et al*., 2006) RFA and EVLA. (Subramonia and Lees, 2007; Gandhi *et al*., 2010)

The cosmetic aspects of VV treatment are well-recognised and in this series over 90% patients were expecting an improvement in the appearance of their legs. (Baker *et al*., 1995; Michaels *et al*., 2006) As has been reported by others after UGFS, (Barrett *et al*., 2004) 96% of patients experienced such an improvement, and more than 85% of patients had their cosmetic expectations met or exceeded. Again, these data suggest that UGFS is at least as effective as other treatments for VV. (Rautio *et al*., 2002; Gandhi *et al*., 2010)

Perhaps not surprisingly, these favourable physical and cosmetic outcomes translated into a range of significant life-style benefits such as the ability to wear different clothes, improved work performance, and more satisfying social and leisure activities for those that wished them. This supports a number of studies showing that CVD has a greater effect on physical ('what a person can do') rather than mental ('how a person feels') status. (Baker *et al*., 1995; Kurz *et al*., 2001; Kaplan *et al*., 2003; Sam *et al*., 2004a) However, these parameters are obviously interconnected. Thus, UGFS also resulted in improvements in the quality of personal relationships in those patients who were seeking such benefits with the majority having their expectations met or exceeded.

Several studies have demonstrated that conventional SVS, EVLA, RFA and UGFS for VV results in significant improvement in HRQL as determined by validated disease-specific and generic instruments (see **Section 4.1.4**). However, such studies and instruments do not allow patients to express their individual expectations of treatment and to what extent these expectations were met. The present type of study therefore adds value to traditional HRQL research in this patient group by personalising the treatment aims and by reducing the risks of the patient and the

clinician talking at cross-purposes when discussing the risks and benefits of intervention. (Davies *et al*., 1995; Jackson and Kroenke, 2001; Kravitz, 2001; Campbell, 2006; Shepherd *et al*., 2010b)

Although the primary purpose of this study was not to compare UGFS with other treatments for VV, it is worth noting that when overall patient satisfaction has been assessed after SVS it has been found wanting, (Bradbury *et al*., 2000) with only 23% reporting 'complete satisfaction' and 26% reporting being 'very dissatisfied' up to ten years after SVS. (Davies *et al*., 1995) It seems likely that many medicolegal claims following SVS result from a lack of understanding, poor history taking and communication. (Davies *et al*., 1995; MacKenzie *et al*., 2002b; Campbell *et al*., 2002; Ray, 2005; Scurr and Scurr, 2005; Campbell *et al*., 2006; Michaels *et al*., 2006; Campbell *et al*., 2007)

More recently three further RCTs have reported patient satisfaction rates. The first found only 27% (11/41) SVS patients and 57% (27/47) RFA patients to be completely satisfied five weeks after treatment. (Subramonia and Lees, 2010) Pronk *et al*. found 79% and 77% of SVS and EVLA patients would have the treatment done on the other leg if necessary; (Pronk *et al*., 2010) and at two years patient satisfaction rates were 90% and 88% respectively in the SVS and EVLA groups in the final study. (Theivacumar *et al*., 2009b) A further questionnaire study by Gandhi *et al*. found that 151/176 (85.8%) were satisfied with their treatment after endothermal ablation; they also found that patients being treated for recurrent VV were more likely to be dissatisfied (25% versus 8%). (Gandhi *et al*., 2010)

In this study the questionnaires were administered by post. The self-completion method was chosen, rather than a face-to-face or telephone interview to reduce the likelihood of introducing interviewer or social desirability bias. Self-administration, however, could also introduce bias due to respondents' lack of comprehension or motivation. Response rates were good at each time-point (around 80%), and although both questionnaires were available for only 60% of the cohort, this is comparable to other questionnaire studies in VV patients of 59-85%. (Baker *et al*., 1995; Smith *et al*., 1999; Durkin *et al*., 2001; Campbell *et al*., 2007; Gandhi *et al*., 2010; Shepherd *et al*., 2010b) Systematic bias in the loss of respondents is unlikely as those who were unhappy with treatment may be more likely to respond.

In conclusion, we have found that when specifically asked most patients admit to having a wide range of different expectations in relation to their VV treatment. Many of these expectations may be unanticipated by the clinician and thus remain unknown to them unless specifically sought during patient interview. Present data indicate that UGFS is usually able to meet, and often exceeds, these physical and psychosocial needs and expectations six months after treatment. UGFS is, therefore, a highly effective treatment for VV from the patients' perspective.

CHAPTER 5. SUMMARY, CONCLUSIONS AND PROSPECTS FOR FUTURE RESEARCH

5.1 Key findings of this thesis

The aim of this Thesis was to investigate the role of UGFS in the management of CVD and began with two studies of the technical and clinical efficacy of UGFS in the treatment of GSVV (**Chapter 2**). I showed that UGFS was an effective treatment for both primary (**Section 2.1**) and recurrent GSVV (**Section 2.2**). Specifically, UGFS eradicated reflux in almost 100% of patients and left no visible VV in around 90% of legs, similar to EVLA and RFA as reported in meta-analysis. (Van den Bos *et al*., 2009) Although recanalisation rates at 12 months, while superior to those often reported after SVS, were somewhat higher than many report following EVLA or RFA, recanalisation was easily and successfully treated in our patients with a single further treatment. Furthermore, in some studies, less than half of patients with recurrent GSVV were amenable to treatment with either of the catheter-based techniques. (Goode *et al*., 2009) UGFS also has the advantage of being able to eradicate, without any risk of nerve injury, BK-GSV reflux which is well recognised as an important source of recurrent disease. (Theivacumar *et al*., 2009a; van Neer *et al*., 2009)

In **Section 2.3** I found that UGFS was also an effective treatment for primary and recurrent SSVV, eradicating reflux in 100% of cases and leaving no visible VV in over 95% of legs. Recanalisation rates at 12 months were similar to those reported in the literature for SVS, (O'Hare *et al*., 2008b) but higher than that reported by some workers following EVLA. (Desmyttere *et al*., 2010) However, EVLA is only suitable for

around 70% of patients with SSV reflux. (Theivacumar *et al*., 2007) As with GSVV, if recanalisation requiring re-treatment occurs after UGFS, it is quick, safe, and both clinically and cost-effective.

In the final section of **Chapter 2** (**Section 2.4**) I examined the effect of UGFS on CVU healing and recurrence rates. In this small pilot study of 28 legs, I found that 96% of CVU were healed within three months, with only a 7% recurrence rate at 12 months. These results are superior to those reported in the literature for either compression alone or compression combined with SVS, (Barwell *et al*., 2004) and suggest that UGFS is a useful adjunct to compression. Two other small studies have recently reported similarly encouraging results using UGFS to treat SVS in association with CVU, (Hertzman and Owens, 2007; O'Hare *et al*., 2010) and we have recently published the results of a larger study with longer follow-up that reproduces these results. (Pang *et al*., 2010) We offer UGFS to our CVU patients as long as they are able to comply with the post-operative instructions for mobilisation.

Having established the technical and clinical efficacy of UGFS, I went on to examine safety and morbidity (**Chapter 3**). In **Section 3.1** I found that patients undergoing UGFS reported significantly less pain, bruising and analgesia usage, and also returned to normal activities faster than patients treated with SVS. UGFS was also safe with only one DVT and three episodes of blurred vision following 418 treatments. Recovery from UGFS appears to be quicker and associated with less morbidity than SVS and also EVLA and RFA. (Darwood *et al*., 2009; Goode *et al*., 2010; Subramonia and Lees, 2010; Shepherd *et al*., 2010a; Carradice *et al*., 2011) This study has allowed us to give more accurate information about post-treatment recovery to our patients. Taken together with our recently published prospective

series of 977 patients, these data indicate that UGFS is a safe and clinically effective treatment for SVR. (Bradbury *et al*.,2010)

In **Chapter 4** I utilised questionnaires to assess the patient's experience of venous disease and its treatment (patient-reported outcomes). The first study (**Section 4.1**) was designed to examine the changes in HRQL following UGFS for symptomatic VV. I demonstrated that UGFS resulted in significant improvements in both generic (mainly in physical domains) and disease-specific HRQL, and that these improvements continued for at least 12 months after treatment and were comparable to those reported after SVS, EVLA and RFA. (Darwood *et al*., 2008; Theivacumar *et al*., 2008; Rasmussen *et al*., 2010; Christenson *et al*., 2010; Shepherd *et al*., 2010a; Subramonia and Lees, 2010; Carradice *et al*., 2011) To our knowledge, this was the first study to examine changes in HRQL after UGFS and will facilitate further work comparing the cost-effectiveness of different treatments. Interestingly, the improvement in generic HRQL was greater in those patients with symptomatic but uncomplicated VV (for whom treatment would currently not be funded by the NHS in many areas of the UK) than those with VV complicated by skin changes of CVI. (Nasr *et al*., 2008).

In **Section 4.2** I described a qualitative study of patient expectations prior to, and following, UGFS. I observed that the majority of patients, who had undergone standard assessment and counselling, had high expectations of UGFS in terms of its ability to produce symptomatic, cosmetic and lifestyle improvements. Fortunately, the data clearly indicate that UGFS is usually able to meet, and often exceed, these expectations, comparing favourably with SVS, EVLA and RFA. (Theivacumar *et al*., 2009b; Gandhi *et al*., 2010; Subramonia and Lees, 2010; Pronk *et al*., 2010)

5.2 Future work

The work I have presented in this Thesis raises a number of interesting questions worthy of future research:

1. What are the longer-term outcomes of UGFS in terms of recanalisation and re-treatment rates and how do they compare with SVS, EVLA and RFA?

2. What is the optimum UGFS technique? There is much variation in UGFS technique between operators and it seems likely that the technique has not been optimised in terms of foam preparation, delivery and bandaging/compression.

3. What will be the long term healing and recurrence rates for CVU following UGFS?

4. In an era of increasing healthcare rationing within the UK NHS, what is the relative cost-effectiveness of conservative therapy with compression only, SVS, EVLA and RFA over the medium term (5 years)?

CHAPTER 6. PEER-REVIEWED PUBLICATIONS BASED ON THE WORK PRESENTED IN THIS THESIS

6.1 Original papers

KAL Darvall, GR Bate, DJ Adam, SH Silverman, AW Bradbury. Duplex ultrasound outcomes following ultrasound-guided foam sclerotherapy of symptomatic primary great saphenous varicose veins. *European Journal of Vascular and Endovascular Surgery* 2010; 40: 534-539.

KAL Darvall, GR Bate, DJ Adam, SH Silverman, AW Bradbury. Duplex ultrasound outcomes following ultrasound-guided foam sclerotherapy of symptomatic recurrent great saphenous varicose veins. *European Journal of Vascular and Endovascular Surgery* 2011; 42: 107-114.

KAL Darvall, GR Bate, DJ Adam, SH Silverman, AW Bradbury. Medium-term results of ultrasound guided foam sclerotherapy of small saphenous varicose veins. *British Journal of Surgery* 2009; 96: 1268-1273.

KAL Darvall, GR Bate, DJ Adam, SH Silverman, AW Bradbury. Ultrasound-guided foam sclerotherapy for the treatment of chronic venous ulceration: a preliminary study. *European Journal of Vascular and Endovascular Surgery* 2009; 38: 764-769.

KAL Darvall, GR Bate, DJ Adam, AW Bradbury. Recovery, analgesia use, and return to normal activities after ultrasound-guided foam sclerotherapy compared with conventional surgery for varicose veins. *British Journal of Surgery* 2009; 96: 1262-1267.

KAL Darvall, RC Sam, GR Bate, SH Silverman, DJ Adam, AW Bradbury. Changes in health-related quality of life following ultrasound guided foam sclerotherapy for great and small saphenous varicose veins. *Journal of Vascular Surgery* 2010; 51: 913-920. Review published: MA Vasquez, CE Munschauer in *Venous Digest* 2010;**17**(6).

KAL Darvall, GR Bate, RC Sam, DJ Adam, SH Silverman, AW Bradbury. Patients' expectations before and satisfaction after ultrasound-guided foam sclerotherapy for varicose veins. *European Journal of Vascular and Endovascular Surgery* 2009; 38: 642-647. Review published: F Lurie in *Venous Digest* 2010;**17**(7).

6.2 Book chapters

KAL Darvall, RC Sam, AW Bradbury. Signs and symptoms of venous disease. In: *Venous Disease Simplified*. AH Davies, TA Lees, and IF Lane (Eds): tfm publishing, Shrewbury 2006.

KAL Darvall, AW Bradbury. The management of venous ulceration. In: *The Evidence for Vascular Surgery 2nd edition*. JJ Earnshaw, JA Murie JA (Eds): tfm publishing, Shrewbury 2007.

KAL Darvall, AW Bradbury. Long saphenous vein ablation: Foam. In: *Vascular and Endovascular Consensus Update*. R Greenhalgh (Ed): BIBA Publishing, London 2007.

Appendix 1. SF-12 questionnaire (Ware *et al*., 2002)

YOUR GENERAL HEALTH

Instructions: This survey asks for your views about your health. The information will help keep track of how you well you are able to do your usual activities.

Please answer each question by circling one response. If you are unsure about how to answer please give the best answer you can.

1. In general would you say your health is:

Excellent	Very good	Good	Fair	Poor

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

2. Moderate activities such as moving a table pushing a vacuum cleaner or playing golf?

Yes limited a lot	Yes limited a little	Not limited at all

3. Climbing several flights of stairs?

Yes limited a lot	Yes limited a little	Not limited at all

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

4. Accomplished less than you would like YES / NO

5. Were limited in the kind of work or other activities YES / NO

During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. Accomplished less than you would like YES / NO

7. Didn't do work or other activities as carefully as usual YES / NO

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

Not at all	A little bit	Moderately	Quite a lot	Extremely

These questions are about how you feel and how things have been you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:

9. Have you felt calm and peaceful?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Never

10. Did you have a lot of energy?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Never

11. Have you felt down or low?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Never

12. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends relatives etc.)

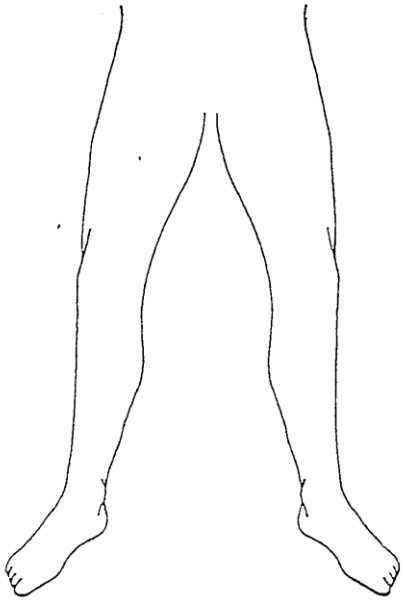
All of the time	Most of the time	Some of the time	A little of the time	Never

Appendix 2. Aberdeen varicose vein symptom severity score (Garratt *et al*., 1996)

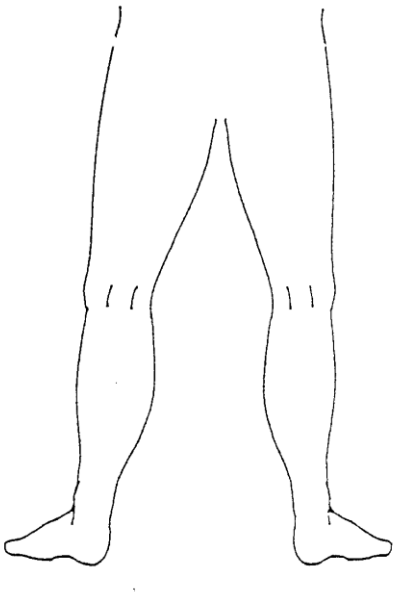
YOUR VARICOSE VEINS

1. Please draw in your varicose veins in the diagram(s) below

Legs viewed from front



Legs viewed from back



2. In the last two weeks, for how many days did your varicose veins cause you pain or ache? (Please tick one box for each leg)

	R leg	L leg
None at all	☐	☐
Between 1 and 5 days	☐	☐
Between 6 and 10 days	☐	☐
For more than 10 days	☐	☐

3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins?
(Please tick one box)

None at all	☐
Between 1 and 5 days	☐
Between 6 and 10 days	☐
For more than 10 days	☐

4. In the last two weeks, how much ankle swelling have you had?
(Please tick one box)

None at all	☐
Slight ankle swelling	☐
Moderate ankle swelling	☐
Severe ankle swelling	☐

5. In the last two weeks, have you worn support stockings or tights?
(Please tick one box for each leg)

	R leg	L leg
No	☐	☐
Yes, those I bought myself without a doctors prescription	☐	☐
Yes, those which my doctor prescribed for me which I wear occasionally	☐	☐
Yes, those which my doctor prescribed for me which I wear every day	☐	☐

6. In the last two weeks, have you had any itching in association with your varicose veins?
(Please tick one box for each leg)

	R leg	L leg
No	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Both above and below the knee	☐	☐

7. Do you have purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins?
(Please tick one box for each leg)

	R leg	L leg
No	☐	☐
Yes	☐	☐

8. Do you have a rash or eczema in the area of your ankle?
(Please tick one box for each leg)

	R leg	L leg
No	☐	☐
Yes, but it does not require any treatment from a doctor or district nurse	☐	☐
Yes, and it requires treatment from my doctor or district nurse	☐	☐

9. Do you have a skin ulcer associated with your varicose veins?
(Please tick one box for each leg)

	R leg	L leg
No	☐	☐
Yes	☐	☐

10. Does the appearance of your varicose veins cause you concern?
(Please tick one box)

No	☐
Yes, their appearance causes me slight concern	☐
Yes, their appearance causes me a great deal of concern	☐

11. Does the appearance of your varicose veins influence your choice of clothing including tights?
(Please tick one box)

No	☐
Occasionally	☐
Often	☐
Always	☐

12. During the last two weeks have your varicose veins interfered with your work / housework or other daily activities?
(Please tick one box)

No	☐
I have been able to work, but my work has suffered to a slight extent	☐
I have been able to work, but my work has suffered to a moderate extent	☐
My veins have prevented me from working for one day or more	☐

13. During the past two weeks, have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)?
(Please tick one box)

No	☐
Yes, my enjoyment has suffered to a slight extent	☐
Yes, my enjoyment has suffered to a moderate extent	☐
Yes, my veins have prevented me from taking part in any leisure activities	☐

Appendix 3. Foam Sclerotherapy Recovery Questionnaire

Please answer the following questions about your recovery after your foam injections for varicose veins. Please circle one answer for each question.

Did you have any bruising after your foam injections?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the bruising last?	Less than 1 week	1-2 weeks	2-4 weeks	More than 4 weeks	
Did you have any pain in your leg after your foam injections?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the pain last?	First 1-2 days only	3-7 days	1-2 weeks	2-4 weeks	More than 4 weeks
Did you have any itching after your foam injections?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the itching last?	First 1-2 days only	3-7 days	1-2 weeks	2-4 weeks	More than 4 weeks
Did you notice any 'lumpiness' in your legs following your foam injections?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the 'lumpiness' last?	Less than 1 week	1-2 weeks	2-4 weeks	More than 4 weeks	
Did you have any problems with your eyesight following your foam injections?	Yes	No			
If so, please write what problem you had, and how long it lasted for.					

How long after your foam injections did you return to work?	I don't go out to work	Same day	Next day	2-4 days later	5-7 days later	7-14 days later	More than 14 days later
What kind of work do you do?	I don't go out to work	Mostly sitting	Sitting and standing	Mostly standing	Very active (lifting etc.)		
When did you return to driving?	I don't drive	Same day	Next day	2-4 days later	5-7 days later	7-14 days later	More than 14 days later
Did you take any painkillers for your leg following your foam injections?	None at all	Same day only	For the first 2 days only	For 2-4 days after	For 5-7 days after	For 7-14 days after	For more than 14 days after

If you have any further comments please write them below. Thank you

Appendix 4. Varicose Vein Surgery Recovery Questionnaire

Please answer the following questions about your recovery after your recent surgery for varicose veins. Please circle one answer for each question.

Did you have any bruising after your varicose vein surgery?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the bruising last?	Less than 1 week	1-2 weeks	2-4 weeks	More than 4 weeks	
Did you have any pain in your leg after your varicose vein surgery?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the pain last?	First 1-2 days only	3-7 days	1-2 weeks	2-4 weeks	More than 4 weeks
Did you have any itching after your varicose vein surgery?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the itching last?	First 1-2 days only	3-7 days	1-2 weeks	2-4 weeks	More than 4 weeks
Did you notice any 'lumpiness' in your legs after your varicose vein surgery?	None	A little	Quite a bit	A lot	An awful lot
If yes, how long did the 'lumpiness' last?	Less than 1 week	1-2 weeks	2-4 weeks	More than 4 weeks	

Please turn over

How long after your varicose vein surgery did you return to work?	I don't go out to work	Same day	Next day	2-4 days later	5-7 days later	7-14 days later	More than 14 days later
What kind of work do you do?	I don't go out to work	Mostly sitting	Sitting and standing	Mostly standing	Very active (lifting etc.)		
When did you return to driving?	I don't drive	Same day	Next day	2-4 days later	5-7 days later	7-14 days later	More than 14 days later
Did you take any painkillers for your leg following your varicose vein surgery?	None at all	Same day only	For the first 2 days only	For 2-4 days after	For 5-7 days after	For 7-14 days after	For more than 14 days after

If you have any further comments please write them below. Thank you

Appendix 5. Pre-treatment expectations questionnaire

About one in five patients has varicose veins in both legs so we are going to ask you about your symptoms in each leg separately.

RIGHT LEG

If you are going to have foam injections in your RIGHT leg (not necessarily at your first appointment) please answer all questions below by ticking the relevant boxes.

I am expecting my foam injections to get rid of the following symptoms in my RIGHT leg:

	I do not have this symptom	A little	Quite a bit	A lot	An awful lot
Pain/Aching	□	□	□	□	□
Itching	□	□	□	□	□
Tingling	□	□	□	□	□
Cramps	□	□	□	□	□
Restless Legs	□	□	□	□	□
Swelling	□	□	□	□	□
Heaviness	□	□	□	□	□

LEFT LEG

If you are going to have foam injections in your LEFT leg (not necessarily at your first appointment) please answer all questions below by ticking the relevant boxes.

I am expecting my foam injections to get rid of the following symptoms in my LEFT leg:

	I do not have this symptom	A little	Quite a bit	A lot	An awful lot
Pain/Aching	□	□	□	□	□
Itching	□	□	□	□	□
Tingling	□	□	□	□	□
Cramps	□	□	□	□	□
Restless legs	□	□	□	□	□
Swelling	□	□	□	□	□
Heaviness	□	□	□	□	□

Please turn over page

Many people have foam injections to improve the appearance and function of their leg.
Please answer all questions about your leg(s).

	Not at all	A little	Quite a bit	A lot	An awful lot
I am expecting my foam injections to improve the appearance of my varicose veins	□	□	□	□	□
I am expecting my foam injections to allow me to wear different clothes	□	□	□	□	□
I am expecting my foam injections to allow me to do my work better.	□	□	□	□	□
I am expecting my foam injections to improve my relationships.	□	□	□	□	□
I am expecting my foam injections to improve my social and leisure activities.	□	□	□	□	□

Thank you for completing this questionnaire. Please feel free to add any comments:

……...
……
……
……

Please bring this with you to your appointment for your foam injections
Thank you

Appendix 6. Post-treatment expectations questionnaire

Please answer the following questions about any improvement that you have had in your symptoms and activities since your foam injections for varicose veins. Please only consider the leg(s) which you had foam injections on. Please tick the box which most closely matches any improvement you have had.

MY FOAM INJECTIONS HAVE IMPROVED THE FOLLOWING SYMPTOMS IN MY LEGS: *(please tick one box for each symptom)*

	Completely (the symptom has gone)	**A lot**	**Quite a bit**	**A little**	**Not at all**	**The symptom has got worse**	**I never had this symptom**
Pain or ache	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐
Tingling	☐	☐	☐	☐	☐	☐	☐
Cramps	☐	☐	☐	☐	☐	☐	☐
Restless legs	☐	☐	☐	☐	☐	☐	☐
Swelling	☐	☐	☐	☐	☐	☐	☐
Heaviness	☐	☐	☐	☐	☐	☐	☐

MY FOAM INJECTIONS HAVE: *(please tick one box for each statement)*

	An awful lot	**A lot**	**Quite a bit**	**A little**	**Not at all**
Improved the appearance of my varicose veins	☐	☐	☐	☐	☐
Allowed me to wear different clothes	☐	☐	☐	☐	☐
Allowed me to do my work better	☐	☐	☐	☐	☐
Improved my relationships	☐	☐	☐	☐	☐
Improved my social and leisure activities	☐	☐	☐	☐	☐

If you have any comments please feel free to add them overleaf. Thank you.

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