# Optimising Outcomes in the Treatment of Superficial Venous Insufficiency

## Mr Tom Wallace

BSc (Hons), MBChB (Honours), MRCS, PGCert Vascular Ultrasound (Dist$^{n}$)

## MD

## The University of Hull and The University of York

## Hull York Medical School

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# Abstract

The traditional "gold-standard" treatment for symptomatic SVI affecting the GSV is conventional open surgery and stripping under general anaesthesia. Despite improved QoL and cost-effectiveness when compared to conservative management, conventional surgery is not without drawbacks. Endovenous ablative treatments have been developed, which seek to address some of these limitations. Randomised clinical trial (RCT) data has demonstrated the superiority of endovenous laser ablation (EVLA) over surgery in the short term. Attention is now focused on evaluating its mid- and long-term outcomes, and to further evolve the technique to improve patient outcomes.

In this thesis, five studies were conceived to address two main objectives. Firstly, two-year follow-up of the HELP-1 RCT of EVLA versus conventional surgery was performed to assess clinical, QoL and duplex ultrasound (DUS) outcomes and identify potential for EVLA technique evolution. Four further studies were performed, aimed at improvement of patient outcomes by modification of the EVLA technique via i) pH buffering of tumescent anaesthesia, ii) concomitant treatment of varicosities, and iii) endovenous energy delivery via longer wavelength laser.

Two-year outcomes from the HELP-1 RCT demonstrated continued superiority of EVLA over conventional surgery in terms of lower clinical recurrence rates, with maintained improvements in clinical and QoL outcomes. DUS outcomes identified patterns of clinical recurrence that can be addressed by simple modifications of the EVLA technique.

Buffering of tumescent anaesthesia resulted in significantly reduced patient-reported periprocedural pain. Concomitant treatment of varicosities with ambulatory phlebectomy under tumescent anaesthesia demonstrated significant benefits in clinical severity and disease-specific QoL over foam sclerotherapy. Use of longer laser wavelength (1470nm) resulted in significantly reduced postprocedural pain in comparison to shorter (810nm) wavelength.

EVLA is demonstrated to have significant short- and medium-term benefits over conventional surgery. Further evolution of the technique, including the modifications described, should provide additional benefit in terms of patient outcomes.

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# Author's Declaration

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# Chapter 1: Introduction

## Opening Statement

Superficial Venous Insufficiency (SVI) refers to disease of the superficial veins of the lower limb, resulting in a range of signs and symptoms from small thread veins, through to uncomplicated varicose veins, chronic skin changes and ultimately ulceration. It is part of a wider spectrum of Chronic Venous Disease (CVD), which also encompasses abnormalities and diseases of the deep veins in the lower limb.

SVI is a common problem and accounts for a significant financial burden on healthcare systems. Affected individuals report a number of symptoms and impaired health-related quality of life (QoL).

A multitude of treatment strategies have been developed, with proven benefits over conservative management. The most significant recent developments have involved endoluminal superficial venous ablation procedures. Within these ablative treatments, endovenous laser ablation (EVLA) has a significant evidence base in the short-term, and has also undergone substantial evolution of technology and technique. The work carried out for this MD is aimed at continuing the long-term follow up of EVLA in comparison to conventional surgery, and seeking to optimise the existing treatment strategies within EVLA to give the best possible outcome for patients.

The following introductory chapter aims to contextualise the subject and outline the background to the work presented in this thesis. This begins with a discussion of the relevant anatomy, pathophysiology, epidemiology and classification. The impact of the problem is then addressed, along with an outline of the current evidence-base for treatment, and important areas of research yet to be undertaken.

## 1.1   The Lower Limb Venous System

### Anatomy, Etymology and Nomenclature

The peripheral venous system acts as both a storage system and conduit to return blood to the heart.  The veins of the lower limb are divided into superficial and deep venous systems, connected by a series of perforator veins and two main "junctions".

The deep venous system of the lower limb is located deep to the muscular fascia and is the primary venous outflow from the limb.  It consists of intramuscular veins and axial veins, which follow the course of the major arteries.  Within the calf muscles, venous plexi form from the joining of venous sinusoids. Paired calf veins, corresponding to the axial arteries, then merge to form the popliteal vein behind the knee.  Upon passing proximally through the adductor canal, it becomes known as the femoral vein; to remove any misconception or doubt that this is a deep vein, the old term *superficial femoral vein* has been replaced by the new term *femoral vein*[1].  The femoral vein is joined by the profunda femoris (deep femoral) vein in the proximal thigh to form the common femoral vein, and eventually the external iliac vein as it passes deep to the inguinal ligament in the groin.  Within the pelvis, the external and internal veins unite on each side to become the common iliac veins, which themselves unite to form the inferior vena cava (IVC) at the level of the fifth lumbar vertebra.

The superficial venous system is located superficial to the muscular fascial layer. It is comprised of an interconnecting network of collecting veins, acting as tributaries to the axial superficial veins, which return blood to the deep venous system via two main junctions and a number of perforating veins in the thigh and lower leg that pierce the muscular fascia[2].  There are two fundamental superficial axial veins of the lower extremity, the great saphenous vein (GSV) and small saphenous vein (SSV).  These veins lie within their own compartment bounded by the muscular fascia below and the saphenous fascia above.  These principle superficial trunks are fed by an extensive network of tributary vessels from within the superficial tissues of the leg.  It is these tributary vessels that give rise to the appearance of "varicose veins", "reticular veins" and "telangiectasia" in the diseased state (see Classification of SVI, p.32); the main superficial trunks themselves may also be varicose.

The GSV is the longest vein in the human body. It originates on the medial aspect of the foot from the dorsal venous arch, passes anterior to the medial malleolus of the ankle and follows a course in the medial calf and thigh to the groin. At this point the GSV pierces the deep (cribriform) fascia to join the common femoral vein (CFV) at the saphenofemoral junction (SFJ), typically located some 3-4cm inferolateral to the pubic tubercle. The SFJ region also receives tributaries from other superficial veins in the thigh and the venous drainage from parts of the groin, abdominal wall and external genitalia. Commonly found SFJ tributaries are: -

- Superficial inferior epigastric vein
- Superficial circumflex iliac vein
- Superficial external pudendal vein
- Anterior, Posterior and Superficial accessory great saphenous veins
- Anterior and Posterior thigh circumflex veins

These tributaries typically feed into the proximal segment of GSV, but the precise anatomy of this area is highly variable[3], with large-scale operative dissection-based research identifying vastly differing configurations and numbers of SFJ tributaries[4].

The SSV is the second largest superficial vein of the lower limb and originates from the lateral aspect of the dorsal venous arch of the foot. It passes posterior to the lateral malleolus and runs superiorly in the posterior aspect of the calf, in close proximity to the sural nerve, to join the popliteal vein at the saphenopopliteal junction (SPJ) by piercing the deep (popliteal) fascia, usually just proximal to the level of the knee crease. Like the GSV, the anatomical course of the SSV, SPJ and other tributaries are also highly variable[3,5-7].

The healthy adult GSV is typically 3-4mm in diameter, while the SSV usually measures around 3mm in diameter. All superficial and deep veins of the lower limb contain a number of one-way bicuspid valves to prevent retrograde flow (reflux) of blood down the leg with gravity (see Normal Venous Physiology, p.20).

There are more valves in the lower limb than in the upper limb, and valves are more frequently encountered below the knee, which reflects the greater hydrostatic forces exerted in the lower limb with gravity. The GSV has a median of 6 valves with a range of 4-25 in its full length; 85% of people have a valve within 2-3cm of the SFJ[8].

The SSV has a median of 7 valves, with a range of 4-13. The deep venous system has relatively fewer valves than its superficial counterpart, with the common femoral or external iliac vein having only one valve in about 63% of cases[9]. In 37%, there is no valve in the common femoral or external iliac veins. The internal iliac vein has a valve in 10%, while its tributaries have valves in 9%[10].

The superficial axial veins also communicate with the deep venous system through a number of perforating veins, which again, vary greatly in their presence and location.

A further understanding of the superficial venous anatomy can be gained through an understanding of its etymology. It is said that the word *"saphenous"* derives from the Greek word *"safaina"*, the feminine form of the adjective *"safes"*, which means *"evident"*. This relates to the fact that the distal GSV is typically visible and/or palpable just below the skin; it is reported that the ancient Greeks only had an awareness of this distal part of the vein[11].

There is an alternative suggestion; through the practice of therapeutic bleeding, ancient Arabic physicians also knew the anatomy of superficial veins. When treating diseases of the lower abdomen and pelvis, Arabic physicians performed phlebotomy on the distal portion of the GSV at the ankle. The proximal portion of the GSV was called *"el safin"*, or *"the concealed"*. The trunk or the proximal portion of the GSV was considered unsuitable for therapeutic bleeding as it was not clearly evident as a target for phlebotomy[11].

The ultrasonographic appearances of the venous system help to further exemplify the anatomy. In cross-section, the GSV (or SSV) bears resemblance to an eye (Figure 1) (see Duplex Ultrasonography, p.47, for further discussion of this imaging modality).
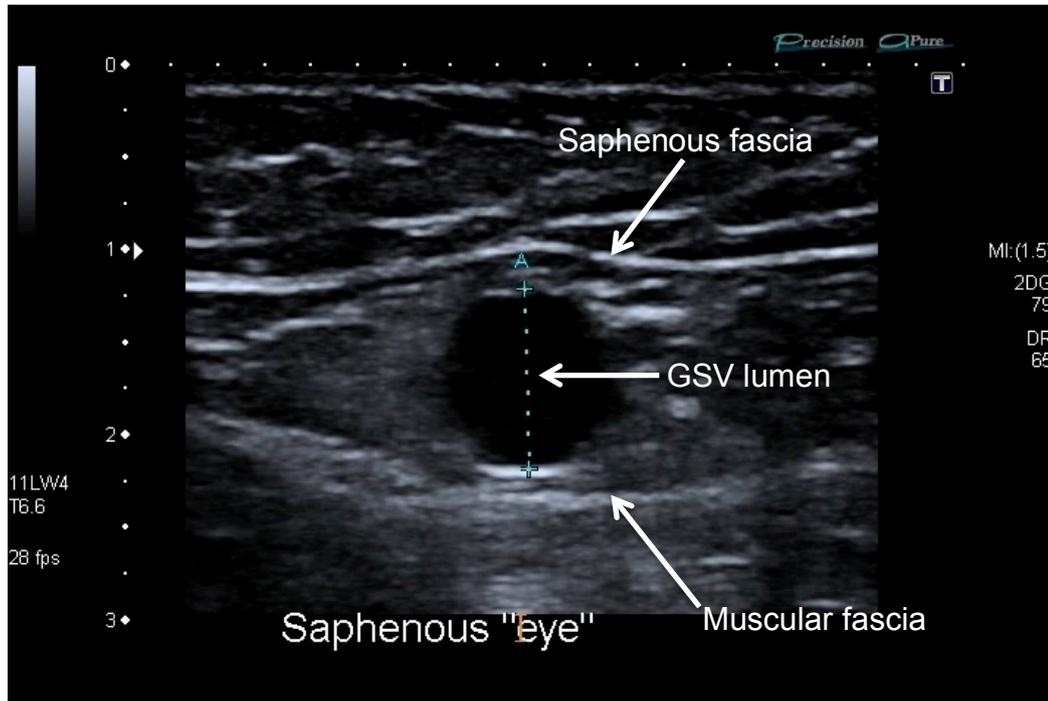
**Figure 1: Transverse B-mode ultrasound image of the GSV**

The terminology for the superficial and deep venous systems of the lower limb has historically been confused by multiple synonyms, anatomically imprecise definitions, eponyms and unnamed vessels. The superficial venous nomenclature has recently been the subject of international consensus documents in order to standardise reporting, aiding direct comparisons between studies and effective dissemination of knowledge[1,12,13] (Table 1). The updates have been approved by the Federative International Committee on Anatomical Terminology (FICAT) to be included in the next update of the *Terminalogia Anatomica[14]* (TA), the official Latin anatomical nomenclature[3]. Much of this work has been based on recent findings from DUS, clinical classification systems and new treatments within the context of SVI[3]. Anatomical terminology used within this thesis will conform to these latest standards.

| Latin Term | Correct English Term | Common obsolete synonyms |
|---|---|---|
| **Vena Saphena Magna** | Great saphenous vein | Long saphenous vein; greater saphenous vein, internal saphenous vein |
| **Vena saphena magna accessoria anterior** | Anterior accessory great saphenous vein | Pre-saphenous arch vein (in thigh); anterior saphenous vein of leg; anterior superficial tibial vein; vena arcuata cruris anterior; anterior tributary vein (in leg); anterior calf vein |
| **Vena saphena magna accessoria posterior** | Posterior accessory great saphenous vein | Post-saphenous arch vein (in thigh); posterior leg vein; vena arcuata cruris posterior |
| **Vena saphena magna accessoria superficialis** | Superficial accessory of the great saphenous vein | - |
| **Vena circumflexa femoris anterior** | Anterior thigh circumflex vein | Lateral accessory saphenous vein; anterolateral (superficial) vein of the thigh; anterior lateral tributary; anterior femoral cutaneous vein; vena semicircularia anterior; ramus descendens lateralis anterior |
| **Vena circumflexa femoris posterior** | Posterior thigh circumflex vein | Medial accessory saphenous vein; posteromedial (superficial) vein of the thigh; posteromedial thigh vein; posterior medial tributary; large accessory saphenous vein; Cruveilhier's vein; cutaneo-femoral superficial interna vein; vena semicircularia posterior; ramus descendens lateralis posterior |
| **Vena saphena parva** | Small saphenous vein | Short saphenous vein; external saphenous vein; lesser saphenous vein; little saphenous vein; peroneo-malleolar vein |
| - | Giacomini's vein | Vena giacomini; vena Giacomini; vena femoralis posterior; vena saphena accessoria medialis |

**Table 1: Terminalogia Anatomica**

Correct English term and obsolete synonyms for common, clinically relevant superficial veins

## Normal Venous Physiology

A series of valves and muscle pumps are fundamental to the normal functioning of the lower limb venous system; blood must travel against gravity, fluctuating thoracoabdominal pressures and changes in body position to return to the central venous circulation and on to the heart[2].

The major driving force of venous blood flow is contraction of skeletal muscle, so-called "venous muscle pumps", primarily in the gastrocnemius and soleus muscles of the calf but also in the foot and thigh. Muscular contraction forces blood out of the muscular venous plexi and cranially through the deep venous system because of increased pressure within the fascial compartments[15], which are of relatively fixed volumes. The muscle pumps function in combination with a series of one-way valves, located throughout the deep and superficial veins, which open to permit movement of blood in a cranial direction toward the heart, and close to prevent retrograde flow. Knowledge of the venous valves was reported as early as the 16th century by Charles Estienne, Giovanni Battista Canano, Ludovicus Vassaeus and further revealed by Fabricius ab Aquapendente[16,17]. It is this knowledge of venous valve function that enabled William Harvey to develop the modern understanding of the circulatory system in the 17th century, completely rewriting the previously held concepts based on the work of Galen dating back to the 2nd century AD.

Venous flow is normally pulsatile and laminar; venous valves open and close approximately 20 times per minute while a person is standing. When the valve leaflets are fully open, they do not touch the vein wall, but create a "sinus pocket". Flow through the valve separates into a proximally directed jet and vortical flow into the sinus pocket behind the valve cusps; the vortical flow prevents stasis in the pocket and ensures that all surfaces of the valve are exposed to shear stress. Valve closure occurs when the pressure caused by the vortical flow exceeds the pressure on the luminal side of the valve leaflet because of the proximally directed jet. Thus minimal reflux occurs, all endothelial surfaces are exposed to a degree of shear stress and are not generally exposed to reverse blood flow[18].

As discussed earlier the lower limb venous valves, typically first located in the common femoral vein or occasionally the external iliac vein, increase in frequency from the proximal to the distal lower limb. This prevents increasing hydrostatic

pressure within the distal veins due to the effects of gravity; perforating veins also contain valves that prevent reflux of blood from the deep to superficial venous systems during contraction of the muscles (muscular systole). The deep venous system is emptied by muscle pump function; hence immediately after ambulation the lower limb venous pressure is normally low (15-30 mm Hg). During muscular diastole (relaxation), there is a relative pressure gradient from the superficial venous system to the emptied deep system. The perforator valves thus open to allow the superficial system to drain into the deep system. With prolonged muscle pump inactivity, the veins slowly fill and distend, allowing the valves to open and eventually increase pressure that is directly related to the height of the column of blood[2]; this may be upwards of 90-100mm Hg. Contraction of the muscle pump will again empty the veins and reduce venous pressure; even subtle activity of skeletal muscle is sufficient to promote flow in a normal individual.

## 1.2 Superficial Venous Insufficiency

Failure of this system of haemodynamic and mechanical mechanisms will result in venous insufficiency; abnormal retrograde flow (reflux) of blood, resulting in venous hypertension, which may affect either the deep (deep venous insufficiency, DVI), superficial (superficial venous insufficiency, SVI), or both (mixed venous insufficiency) venous systems.

### Pathophysiology

#### *Primary Superficial Venous Insufficiency*

"Primary" or idiopathic SVI, reflux where no identifiable underlying cause is seen, accounts for over 80% of patients with the disease[19], and is the focus of this thesis. Other causes less commonly encountered are:-

- Congenital
  - Klippel-Trenaunay Syndrome
  - Parkes-Weber Syndrome

- Secondary
  - Obstruction
    - Mechanical
      - Thrombosis (most common)
      - May-Thurner Syndrome
      - Nutcracker Syndrome
      - Tumour
      - Trauma
      - Iatrogenic
    - Functional (Failure of muscle pump)
  - Arteriovenous fistula

Any impediment to the normal contraction of the calf muscle pump may significantly reduce active propulsion of venous blood from the calf sinusoids and thereby lead to venous hypertension in the presence of otherwise (initially) normal veins and valves. Similarly, reduced lower limb mobility from a congenital, orthopaedic or neurological

condition or any other condition that leads to a wheelchair-bound state will also reduce the contractile capacity of the calf muscles and cause pump failure[20].

SVI is more common than DVI or mixed venous insufficiency, with the GSV most commonly affected. In a study of women with uncomplicated varicose veins, GSV disease was present in two-thirds (isolated in 60%). SSV disease was present in 20% (only 3% had isolated SSV reflux). 23% had perforator reflux, while DVI was only seen in 2%[21]. Studies of isolated SVI have shown the same patterns of distribution; 67-86% of patients have GSV insufficiency (48-60% in isolation) and 3-33% have isolated insufficiency of the SSV. It has not been fully elucidated why the GSV is affected more commonly than the SSV, although it has been suggested that this may be due to the greater number of tributaries draining into the GSV and the higher concentration of valves per unit length in the SSV[22,23].

DUS studies of patients with venous ulceration suggest that approximately 50% have isolated SVI; 32% to 44% have mixed incompetence of both superficial and deep systems, 5% to 15% have reflux in the deep system alone and a minority of patients (2% to 5%) have isolated incompetence of a perforator vein[24,25].

Even in the context of previous DVT, while the likelihood of DVI is higher (38% versus 11% for non-DVT patients), the majority of patients (56%) have either mixed or isolated superficial reflux[25]. In 1992, Darke demonstrated that over one third of patients with venous ulceration have isolated SVI with or without perforator incompetence, without any DVI[26]. Thus, up to 98% of patients with uncomplicated SVI and 85% of patients with the most severe disease have a superficial venous target for treatment.

Examining the patterns of reflux in primary SVI has given rise to debate regarding its pathogenesis and progression. Underpinning the overall theory, however, is the observation of venous hypertension through incompetent venous valves[18].

The "Saphenocentric", or "Descending" theory asserts that reflux begins with valve failure at the saphenous junctions, followed by progressive retrograde propagation of reflux as more distal valves become incompetent due to back-pressure of the column of blood from above. Venous stasis and hypertension damage the vein wall to create further dilatation and weakness. This is the classical hypothesis and its origins can be

traced back to Paulus of Aegina[27] in the 7th century AD, with further dissemination by Trendelenburg[28].

The descending saphenocentric theory has been challenged, with fairly strong evidence. It was pointed out as early as 1870 that many patients with varicose veins have normal saphenous trunks[27]. A number of studies have shown that either one or both of the junction and axial superficial vein are competent in many limbs with varicosities[21,29-31], giving rise to an alternative "ascending" theory of pathogenesis. The role of perforators in SVI adds an extra level of complexity[32], and observation of patients with distal disease in the presence of normal proximal veins suggests that SVI will progress both distally and proximally[33]. Labropoulos *et al*[34] proposed that the origin of venous reflux in patients with primary varicose veins can be local or multifocal structural weakness of the vein wall and that this can occur together or independently of proximal valvular incompetence.

DUS has been invaluable in elucidating these vagaries of haemodynamics and the different patterns of reflux in SVI[27]. It is apparent from an increasing number of studies and emerging theories of pathogenesis, however, that haemodynamic changes alone are not the sole explanation for development of SVI. A simple (perhaps oversimplified) example of this is the observation that normal vein used as arterial bypass conduit does not become varicose[35,36].

The pathophysiology of primary SVI now appears to comprise an intricate interplay between haemodynamics, biochemical pathways and structural elements of vein wall and valve; it is considered a multifactorial process, which is yet to be fully elucidated. There are numerous described genetic, hormonal and mechanical risk factors[37]; the situation is almost akin to the "chicken and egg" quandary, with suggestion of a vicious cycle or "pernicious loop"[38] of disease (Figure 2).
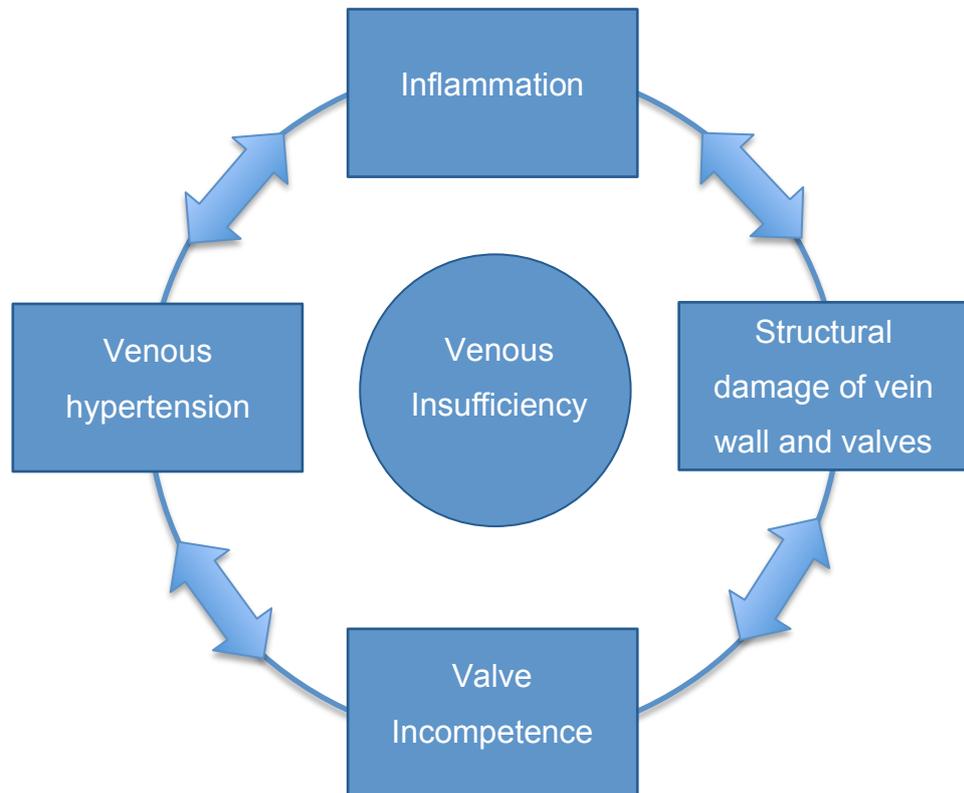
**Figure 2: Vicious cycle of SVI Pathophysiology.**

Adapted and simplified from[18]

A significant finding relevant to the embryology of the venous valves in 1926 stated that the valves were thickenings of the endothelium[16], which receives nutrition directly via the luminal blood stream. Hence, when the blood-flow decreases, such as in venous stasis, valves will ultimately atrophy. In 1937, Edwards and Edwards[39] described the damaging effects of thrombophlebitis on the venous valve and its consequences in the development of venous insufficiency[39].

Strong evidence indicates that venous insufficiency is an inflammatory disease[18], but the mechanism triggering the inflammatory cascade is yet to be determined; a series of events such as the presence and proliferation of dilated veins and capillaries[40], hypoxia[41], low shear stress and increased stretch[42-44] and many others have been demonstrated.

Varicose vein walls and valves are known to have several differences within their cellular and extra-cellular composition compared to those of normal veins. Rather than following a progressive change, the differences seem to occur in a random pattern[43] and affect all layers of the vein wall. These changes include areas of irregular

hyperplasia, deposition of collagen, smooth muscle cell infiltration and proliferation[45], degradation of the extracellular matrix and migration of inflammatory cells.

Remodeling of tissue is a normal, dynamic process; a fine balance between proteases and their inhibitors, the most notable of which are matrix metalloproteinase enzymes (MMPs) and tissue inhibitors of MMPs (TIMPs)[46]. Both clinical and basic scientific research studies suggest a role of MMPs, which are produced by inflammatory cells, in damaging the endothelial and smooth muscle components of the vein wall. The relationship between MMPs and their tissue inhibitors (TIMPs) is disrupted in varicosities, leading to both extracellular matrix degradation[47,48] and hypertrophy; an increase in MMP activity promotes matrix degradation, while an increase in TIMPs has the reverse effect. The consequent change in matrix components is also reflected in vein wall morphology due to the changes in basic structural elements. Thus, the observed morphology of varicose vein wall at any time of its development will be the result of such a matrix imbalance, and may be reflected in the expression of MMP and TIMP and vice versa[46]. MMP-9 has also been shown as a marker of venous stasis in SVI[49], thus adding further weight to the arguments both of stasis as a mediator of vein wall injury and of inflammation as part of a vicious cycle.

Endothelial cellular injury and activation increases the expression of inflammatory markers and leucocyte recruitment in varicosities[44]. Then, the injured endothelial cells trigger leucocyte infiltration, activation and inflammation, which lead to further vein wall and valve leaflet damage[48,50], provoking valvular destruction and wall remodelling[18]; this infiltration has been associated with expression of endothelial cellular adhesion molecules such as E-selectin, VCAM-1 and ICAM-1[51,52]. GSV from patients with primary varicose veins taking 300mg day$^{-1}$ ASA for 15 days prior to surgical stripping demonstrated a non-significant trend to reduced chemokine expression[53].

The effect of increased venous pressure has been characterized in an animal model, whereby the creation of a femoral arteriovenous fistula in a rat resulted in significantly elevated venous pressures to approximately 90mm Hg[54-56]. Reflux did not occur until two days later, although the valves were seen to stretch immediately. Subsequently, the levels of inflammatory cells (granulocytes, monocytes, macrophages and lymphocytes) were significantly elevated within the refluxing valves; MMP levels were also elevated. Other studies have also found increased levels of inflammatory

cells (monocytes and macrophages) in the venous valves of "diseased" individuals compared to controls[57]; affected valve leaflets were also significantly shortened  The histological findings of fibrosis, loss of elastic tissue and increasingly distended, tortuous veins was also found in a porcine femoral arteriovenous fistula model[58].

Histological studies have also revealed down-regulation of apoptosis in the medial layer of GSV trunk, tributaries and accessory veins in individuals with primary varicose veins[59].   Lee *et al*[60] identified significantly increased expression of metallothionein and hypoxia-inducible factor-1α, which are implicated in down-regulation of apoptosis in hypoxic conditions, within varicose veins than in controls, which may be a driver of hyperplasia.  Vascular smooth muscle cells (SMCs) are not terminally differentiated, and have been shown to undergo phenotypic switching in association with various abnormal physiological conditions[61].  In SVI, SMCs are seen to dedifferentiate and transform from being normally-contractile to containing collagen-like fibrils, thus contributing to the fibrotic nature and decreased contractility of diseased vein wall [42,45,62,63].  Loss of elastin and type III collagen has been reported in diseased veins[64,65]; others have seen a selective decrease in type III collagen compared to type I collagen[66].  Type I collagen is a rigid, fibrillar protein, while type III has elastic properties[65], similar to elastin; hence the normal elastic nature of the vein wall will further reduce.  Interestingly, deficiency of Type III collagen is the underlying abnormality seen in Vascular (type IV) Ehlers-Danlos syndrome in which sufferers display a high propensity to formation and rupture of aneurysms; early onset varicose veins are one of the minor diagnostic criteria[67].

Impaired venous tone has been implicated in the pathogenesis of SVI.   A pharmacological study of vein wall harvested from varying severities of incompetence has shown different responses to vasoactive substances.  Both normal and incompetent but clinically normal varicose vein segments displayed normal contractility in response to phenylephrine and aescin (horse-chestnut extract).  However, grossly varicose vein segments did not contract in response to these drugs[68].

Under conditions of venous hypertension, endothelial cells release less nitric oxide and vascular endothelial growth factor (VEGF)[69]; altered transcription of VEGF and its receptors has also been implicated in SFJ incompetence [70].

*Genetic links*

There is little doubt that within the multifactorial development and progression of venous insufficiency, there is at least a moderate genetic component. Positive family history in patients with venous disease was recognized well before the turn of the 20th century[71]. However, various epidemiological studies looking at heredity as a risk factor have not found a common ground (see Epidemiology, p.38).

A clinical study of 134 families suggested an autosomal-dominant inheritance with variable penetrance; there was a 90% chance of an individual developing varicose veins when both parents were affected, 25% for men and 62% for women when one parent was affected. There was a 20% risk of sporadic varicose veins when neither parent was affected[72].

To date, only three candidate genes have been implicated in the development of SVI[73]. A rare inherited condition *lymphedema distichiasis*, in which individuals commonly exhibit varicose veins, is due to a FOXC2 gene mutation[74]. A small (n=18) follow-up study by the same group of authors to identify the gene revealed that all participants with the FOXC2 mutation demonstrated superficial venous reflux on duplex ultrasonograpy; all superficial venous valves were affected by the mutation[75]. Patients with venous thrombosis who had the *del TT* allele for the Thrombomodulin gene, which encodes for an endothelial cell surface glycoprotein receptor that binds thrombin[76], were found to be significantly more likely to have varicose veins than those with the wild-type allele. Finally, patients with the C677T methylenetetrahyrofolate reductase (MTHFR) functional polymorphism have been demonstrated to have a higher prevalence of varicose veins than a control group (odds ratio = 1.74, $p < 0.005$)[77].

A degree of caution ought to be taken when interpreting these studies; the finding of varicose veins in the Thrombomodulin study was a *post* hoc analysis, while the other studies had small sample sizes and none of these findings have been replicated by other groups. Such underpowered studies have been shown to be the source of a high level of false-positive association[73]. A 2003 review of epidemiological and genetic aspects of the heredity of varicose veins commented "*the majority of studies identified in the literature suffer from huge methodological biases linked to the method of data collection and to nosological inaccuracies*"[78]; little has changed in this regard.

The extent and rate of progression of the different changes depend on the interplay of these many factors, and no doubt many more that are yet to be discovered, which will produce a wide variation in symptoms, signs and severity of disease among patients.

### *Chronic Venous Insufficiency*

Beyond vessel changes that account for telangiectasia through to varicose veins, a number of further biochemical and structural changes are seen to take place within the soft tissues of the lower limb, which mediate the progression of SVI to more severe clinical presentations such as trophic skin changes and ultimately venous ulceration (see Clinical Presentation and Classification, p.30). The general term for venous insufficiency that has progressed to skin changes is *Chronic Venous Insufficiency* (CVI); both SVI and CVI can be considered under the umbrella term "Chronic Venous Disease" (CVD). As in uncomplicated SVI, the definitive process causing skin changes and ultimately necrosis has not been fully elucidated, although a number of pathophysiological mechanisms have been proposed on how this occurs at a microcirculatory level; ultimately, as discussed earlier, a significant majority of patients with CVI have underlying primary SVI, and inflammation in the context of venous hypertension appears to be underlying key concept.

In a sample of patients with a range in severity of venous disease, there was a linear trend toward more severe skin damage with increasing post-ambulatory venous pressure[79]. An increase in the occurrence of leg ulceration with increasing post-ambulatory venous pressure was also observed in a study of patients with CVI; venous ulceration was absent in all patients with post-ambulatory venous pressures of less than 30 mm Hg, and present in all patients with pressures of more than 90 mm Hg[80].

The most contemporary and widely accepted mechanism linking venous hypertension to both macro- and micro-circulatory changes in CVI is the leucocyte 'trapping' hypothesis, when the leg is dependent and when venous pressure is elevated[81]. It has been shown that blood returning from feet that have been passively dependent for a period of 40 to 60 minutes is depleted of leucocytes, particularly in patients with CVI[81,82]. This finding suggests that leucocytes accumulate in the leg under conditions of high venous pressure. In addition to leucocyte infiltration of the venous wall and valves, as described earlier, they may additionally become trapped in the microcirculation and migrate into the surrounding soft tissue due to a variety of factors such as an inflammatory focus, activation of endothelial cells by hypoxia, or by altered

haemodynamics[51,53,83-85]. Once in the soft tissues, the leucocytes are activated, initiating an intense inflammatory reaction, thought to be responsible for the skin changes[86,87]. The lower limb skin of individuals affected by CVI, demonstrates a relationship between venous hypertension and leucocyte activation. Immunohistological studies have shown an increase in the number of macrophages and T-lymphocytes in lipodermatosclerotic skin[57].

Again, elevated expression and activity of MMPs, particularly MMP-2, and reduced TIMP expression, has been implicated in the skin changes of CVI[88-90]; clearly this will therefore favour a state of extracellular matrix breakdown rather than healing. The skin in CVI appears hyper-pigmented due to increased venous pressure and capillary permeability allowing extravasation of red cells. This leads to elevated levels of ferritin and ferric iron in affected skin[91,92], which may further exacerbate tissue damage and delay healing through oxidative stress and MMP activation[93]. Venous hypertension increases the capillary hydrostatic pressure gradient across the across the capillary wall; coupled with abnormal capillary structure and increased vessel permeability this results in increased movement of plasma into the interstitium, leading to dependent oedema. In addition, the increase in tissue fluid from oedema and inflammation interrupts gas and nutrient exchange between cells and the capillaries[94]. These effects result in induration, skin breakdown and ulcer formation after minor, innocuous trauma or even spontaneously; healing is prolonged or even arrested due to the hostile environment created by these processes.

## Clinical Presentation and Classification

### Signs and Symptoms

As outlined in the discussion of pathophysiology above, SVI results in clinical features that lie on a spectrum of severity. However, this spectrum is neither linear nor continuous and clinical features may not be cumulative or additive; patients may present with severe features of disease in the absence of lesser findings[95].

International consensus[96,97] has defined the clinical signs typical of both SVI and the wider spectrum of CVD (Table 2):-

| Clinical Sign | Synonyms | Description |
|---|---|---|
| **Telangiectasia** | spider veins, hyphen-webs, thread veins | Confluence of dilated intradermal venules less than 1 mm in diameter. |
| **Reticular veins** | blue veins, subdermal varices, venulectasies | Dilated bluish subdermal veins, usually 1mm to less than 3mm in diameter. Usually tortuous. Excludes normal visible veins in persons with thin, pale skin. |
| **Varicose veins** | varicosities, varices, varix | Subcutaneous dilated veins 3mm in diameter or larger, measured in the upright position. May involve saphenous veins, tributaries, or nonsaphenous superficial leg veins. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose |
| **Corona phlebectatica** | malleolar flare, ankle flare | Fan-shaped pattern of numerous small intradermal veins on medial or lateral aspects of ankle and foot. Commonly thought to be an early sign of advanced venous disease. |
| **Oedema** | | Perceptible increase in volume of fluid in skin and subcutaneous tissue. Characteristically indents with pressure. Venous edema usually occurs in ankle region, but may extend to leg and foot. |
| **Pigmentation** | haemosiderosis | Brownish darkening of skin, resulting from extravasated blood. Usually occurs in the ankle region, but may extend to leg and foot. |
| **Venous Eczema** | | Erythematous dermatitis, which may progress to blistering, weeping, or scaling eruption of skin of the leg. Most often located near varicose veins, but may be located anywhere in the leg. |
| **Lipodermatosclerosis** | LDS, "champagne-bottle leg" | Localized chronic inflammation and fibrosis of skin and subcutaneous tissues of lower leg, sometimes associated with scarring or contracture of the Achilles tendon. May be preceded by diffuse inflammatory oedema of the skin, sometimes painful, often referred to as hypodermitis. Must be differentiated from lymphangitis, erysipelas, or cellulitis by their characteristically different local signs and systemic features |
| **Atrophie Blanche** | white atrophy | Localized, circumferential whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. Sign of severe CVD, and not to be confused with healed ulcer scars. |
| **Venous ulcer** | stasis ulcer | Full-thickness defect of skin, most frequently in ankle region, that fails to heal spontaneously and is sustained by CVD |

**Table 2: Clinical Signs of CVD**

Symptoms related to SVI or more advanced CVD include tingling / "pins and needles", aching, burning, pain, muscle cramps, swelling, sensation of throbbing or heaviness, itching skin, restless or tired legs, fatigue[98]. These symptoms are strongly suggestive of CVD, particularly if they are exacerbated by heat or dependency noted

during the course of the day and relieved by resting or elevating the legs or by wearing elastic stockings or bandages[99], however they are not entirely pathognomic and so the clinical assessment of patients must also seek to rule out other causes of their symptoms (see 1.3 Assessment of SVI, p.45). Pain during and after exercise that is relieved with rest and leg elevation (venous claudication) can also be caused by venous outflow obstruction caused by previous DVT or by narrowing or obstruction of the common iliac veins (May-Thurner syndrome). Diffuse pain is more frequently associated with axial venous reflux, whereas poor venous circulation in bulging varicose veins usually causes local pain[100].

Additionally, patients may be troubled by further complications of SVI such as thrombophlebitis or bleeding. Whilst generally not considered to be a life-threatening condition, deaths from complications of SVI have been widely documented, typically due to exsanguination from a varicosity after seemingly innocuous trauma[101-106].


### *Classification of SVI*

#### CEAP

As discussed above, the clinical signs consistent with the varying severity of venous insufficiency were defined by international consensus in 1994, with further revision in 2004. Prior to this, definitions varied between studies. The criteria used by the Basle Study were the most comprehensive and widely used for some time; this was a prospective epidemiological field study among 4529 apparently healthy employees of the Basle pharmaceutical industry[107]. The Edinburgh Vein Study, one of the largest epidemiological studies of venous disease, used these original Basle criteria to categorise varicose veins as either "trunk varices", "reticular varices", or "intradermal varices"[108]. However, the latter category was not included in the classification system of other studies. Subsequent classification criteria expanded the Basle criteria to include varicose veins, reticular veins, and telangiectasia[109]. It was becoming an increasingly held view that "venous insufficiency" was a poorly defined term, with various interpretations by different clinicians[107]. More recently, DUS detection of venous insufficiency has further expanded the diagnosis of functional disease within CVD[110], in addition to clinically evident signs. To address these disparities in clinical definition and severity of CVD, the Clinical, aEtiologic, Anatomic, Pathophysiologic (CEAP) classification system was developed in 1994[96], with further refinement in 2004[97].

The CEAP system, a physician-generated classification tool, is now generally accepted as the most appropriate means of classifying CVD[100]. The system can be used in a "basic" form, as shown in Table 3, or in "advanced" form by the addition of information on the specific venous segments involved in disease (Table 4), the date of examination and the "Level" of investigation utilised (Table 5).

| CEAP | Description |
|---|---|
| **C**linical classification | |
| $C_0$ | No visible or palpable signs of venous disase |
| $C_1$ | Telangiectases or reticular veins |
| $C_2$ | Varicose veins |
| $C_3$ | Oedema |
| $C_{4a}$ | Pigmentation and / or eczema |
| $C_{4b}$ | Lipodermatosclerosis and / or atrophie blanche |
| $C_5$ | Healed venous ulcer |
| $C_6$ | Active venous ulcer |
| Each clinical classification can be given a suffix of "S" or "A" for symptomatic or asymptomatic respectively. | |
| | |
| a**E**tiologic classification | |
| $E_c$ | Congenital |
| $E_p$ | Primary |
| $E_s$ | Secondary |
| $E_n$ | No venous aetiology identified |
| | |
| **A**natomic classification | |
| $A_s$ | Superficial veins |
| $A_p$ | Perforator veins |
| $A_d$ | Deep veins |
| $A_n$ | No venous location identified |
| | |
| **P**athophysiologic classification | |
| $P_r$ | Reflux |
| $P_o$ | Obstruction |
| $P_{r,o}$ | Reflux and obstruction |
| $P_n$ | No venous pathophysiology identified |

**Table 3: Basic CEAP Classification of CVD**

Modified from[97]

| Numbered Venous Segments | |
|---|---|
| **Superficial veins** | |
| 1: Telangiectases or reticular veins | 4: SSV |
| 2: GSV above knee | 5: Nonsaphenous veins |
| 3: GSV below knee | |
| | |
| **Deep veins** | |
| 6: IVC | 12: Deep femoral vein |
| 7: Common iliac vein | 13: Femoral vein |
| 8: Internal iliac vein | 14: Popliteal vein |
| 9: External iliac vein | 15: Crural: anterior tibial, posterior tibial, peroneal veins |
| 10: Pelvic: gonadal, broad ligament veins, other | 16: Muscular: gastrocnemial, soleal, other |
| 11: CFV | |
| | |
| **Perforating veins** | |
| 17: Thigh | 18: Calf |

**Table 4: Named venous segments used in the advanced CEAP system**

| Level of Investigation | Description |
|---|---|
| **Level I** | Office (clinic) visit, with history and examination. May involve the use of hand-held doppler |
| **Level II** | Non-invasive vascular laboratory testing. Routinely includes DUS; plethysmography added as and when desired/ indicated |
| **Level III** | Invasive investigations or more complex imaging studies; venography, pressure measurements, CT/MRI |

**Table 5: Level of investigation within the CEAP system**

As an example, a patient presenting with primary symptomatic varicose veins, ankle oedema and venous eczema, with reflux identified on DUS in the above and below knee GSV on 10th March 2011, would be classified as below: -

- Basic CEAP: $C_{4a, S}, E_p, A_s, P_r$
- Advanced CEAP: $C_{2,3, 4a, S}, E_p, A_s, P_{r2,3}$ (10/03/2011, LII)

Guidelines suggest use of the basic CEAP for routine clinical practice, with the advanced form being a useful tool in research[100]. In real-world use, patients tend to be labeled according to their highest presenting clinical classification only; validation of CEAP has also often only focused on the clinical classification[95].

There are, however, some inherent limitations of the CEAP classification; venous disease is a chronic condition that comprises an evolving spectrum of symptoms and severity, and change in status following therapy is an ongoing process[13]. Many of the clinical components are relatively static and not sensitive to change following treatment; a patient with a venous ulcer, even though healed, cannot move below C5 regardless of the degree of improvement produced by successful treatment. The fibrotic and pigmentation aspects of $C_4$ disease are also unlikely to change once developed, regardless of the success of treatment in addressing underlying reflux and other signs or symptoms. Meanwhile, a patient with a single varicosity arising from a non-saphenous origin in the lower leg will be graded as $C_2$, the same as a patient with widespread varicose veins arising from all superficial trunks throughout the entire limb; the degree of severity is similarly not delineated or stratified within the other clinical classes. The designation of clinical status as either "asymptomatic" or "symptomatic" clearly does not give an indication of the differences in severity of symptomatology either within the same patient over time, or between patients. Furthermore, the *E-A-P* components of the classification use alphabetical designations that are thus not quantifiable. Therefore, while CEAP is quite valuable in comparing patient mix and establishing a starting point before treatment, it does not fulfill the broader requirements of venous outcomes assessment[111], particularly after treatment[112].

### Venous Clinical Severity Score

To complement CEAP, and address the need for standardised venous testing, the committee on Venous Outcomes Assessment of the American Venous Forum developed the Venous Clinical Severity Score (VCSS) system[113], with further refinement in 2010[114] (Table 6). It is a physician-led assessment of nine clinical signs or symptoms of CVD, including pain, the presence and severity of varicose veins, oedema and signs of CVI, plus a tenth category for patient compliance with compression therapy. The VCSS correlates well with the CEAP score and with the severity of venous reflux or obstruction on DUS[114-116]. Several studies have proven the VCSS as a reliable and responsive evaluation of patient outcomes in terms of change in symptoms, signs and disease status over time and after treatment[115-118].

There are aspects of the VCSS that have attracted criticism, however. One such area surrounds the inclusion of compliance with compression therapy. As will be discussed in detail later (see 1.4.1 Compression, p.55), the utility, value and methods of compression have been subject to a range of opinion according to various differing sources of clinical evidence. Simple modification of clinical advice to patients regarding compression could hence significantly influence the VCSS score between otherwise identical patients. Additionally, the reporting of pain, whilst recorded by the physician, is based upon subjective patient reporting. Notwithstanding these criticisms, the VCSS is recommended by international guidelines as a means of evaluating patients with SVI[100].

| Attribute | Score | | | |
|---|---|---|---|---|
| | **None: 0** | **Mild: 1** | **Moderate: 2** | **Severe: 3** |
| **Pain** (or other discomfort – aching, heaviness, fatigue, soreness, burning) | None | Occasional. Not restricting daily activity | Daily. Interfering with, but not preventing regular daily activities | Daily. Limits most regular daily activities |
| **Varicose veins** | None | Few: scattered(i.e isolated branch varicosities or clusters, also includes corona phlebectatica | Confined to either calf or thigh | Involve calf and thigh |
| **Oedema** Presumes venous origin | None | Limited to foot and ankle area | Extends above ankle, but below knee | Extends to knee and above |
| **Skin pigmentation** Presumes venous origin; does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases | None or focal | Limited to perimalleolar area | Diffuse over lower 1/3 of calf | Wider distribution above lower 1/3 of calf |
| **Inflammation** More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis) | None | Limited to perimalleolar area | Diffuse over lower 1/3 of calf | Wider distribution above lower 1/3 of calf |
| **Induration** LDS and atrophie blanche | None | Limited to perimalleolar area | Diffuse over lower 1/3 of calf | Wider distribution above lower 1/3 of calf |
| **No. of active ulcers** | 0 | 1 | 2 | ≥3 |
| **Duration of longest active ulcer** | - | <3mths | >3mths but <1yr | >1yr |
| **Diameter of largest active ulcer** | - | <2cm | 2-6cm | >6cm |
| **Compression therapy** | Not used | Intermittently used | Worn most days | Full compliance |

**Table 6: The revised Venous Clinical Severity Score (VCSS) system.**
Adapted from[114]

## Scale and Burden of the Disease

### Epidemiology

SVI is a common problem; varicose veins, just one aspect of this spectrum of disease, are the most frequently diagnosed vascular abnormality[115]. They have been cited as the seventh most common reason for seeking medical advice in both the USA[119] and France[120]. The literature contains many epidemiological studies of SVI and CVI, but even the most recent are at least over a decade old and many are significantly older. These studies use a range of differing epidemiological terms, making comparison between them difficult. Imprecise terms such as "occurrence" and "frequency" were commonly reported in earlier papers, rather than generally accepted epidemiological terms such as *incidence* and *prevalence*.

Incidence is the number of patients with the onset of the condition over a specific time period. The Framingham Heart Study reported the annual incidence of varicose veins as 2.6% in women and 1.9% in men[121].

Prevalence can be classified as "point prevalence" – the number of patients with a condition at a single point in time, or "period prevalence" - the number of patients with the condition over a period of time. The point prevalence of uncomplicated varicose veins is estimated to be between 10-25% of the adult population[119], but estimations vary widely from 2% to 56% in men and from less than 1% to 73% in women[107].

The Edinburgh Vein Study[108], a cross-sectional study of a random sample of 1566 subjects 18 to 64 years of age from the general population in Edinburgh, reported telangiectasia and reticular veins in approximately 80% of men and 85% of women. Varicose veins were present in 40% of men and 16% of women, whereas oedema was present in 7% of men and 16% of women.

The Bonn Vein Study[31] enrolled 3072 randomly selected participants (1722 women and 1350 men), aged from 18 to 79 years. It reported symptoms of venous insufficiency in 49.1% and 62.1% of men and women respectively. Also reported were varicose veins without oedema or skin changes in 14.3% (12.4% men, 15.8% women), oedema in 13.4% (11.6% men, 14.9% women), skin changes in 2.9% (3.1% men, 2.7% women), and healed or active ulceration in 0.6% or 0.1%, respectively.

A French population-based study[120], originally designed to look at the prevalence of Raynaud's phenomenon, found for men and women respectively: C2 disease in 23.7% and 46.3%, C3 disease in 1.1% and 2.2%, C4 disease in 4.0% and 2.1% and C5 disease in 1.4 and 0.7%; there were no active venous ulcers.

The National Venous Screening Program in the USA screened 2234 Americans for venous disease[122]; in this cohort, the point prevalence of CEAP clinical grades of C0 to C6 were 29%, 29%, 23%, 10%, 9%, 1.5%, and 0.5%, respectively.

The range in prevalence estimations between studies seems to be largely due to factors other than actual differences in population frequency. There have been various subtle differences in the definitions, terminology and classification of venous disease[123-127], as consensus has taken time to develop and evolve over the last few decades. Use of diagnostic imaging, particularly DUS, has had a huge impact on the understanding of the disease and has further evolved over the last 20 years, but even subtle differences in the imaging technique itself can give rise to differing estimates of reflux and its duration, as highlighted by differences between the Edinburgh and Bonn vein studies[31,128]. Composition of study populations in terms of age, race, gender, sampling methodology and geographic location seems to account for most of the other discrepancies between epidemiological estimates[107,119]. It is also important to remember that many patients with SVI, particularly in its early stages, are symptomless and the disease may therefore may be underreported[129]. As SVI can be both chronic and recurrent, there is likely to be a marked difference between incidence, point prevalence and period prevalence[119], particularly between different countries and healthcare systems, where access to and success of treatment may differ significantly. These factors pose considerable problems when attempting to correlate findings from different epidemiological studies even when the terms are adequately defined[119].

*Disease Progression and CVI*

Prevalence estimates of CVI also vary, from 1-17% in men and 1-40% in women. These estimates are highly dependent on the inclusion or exclusion of hyperpigmentation, eczema, and varicose veins as part of the clinical definition[107]. A French epidemiological study estimated the point prevalence of combined C5 and C6 disease to be 0.7% in females and 1.4% in males, while the Edinburgh Vein Study gives an estimate of 0.64%[110].

Information on the progression of uncomplicated primary SVI to more severe CVI and ulceration is not yet completely defined or understood[130], although it is recognised that clinical severity of SVI/CVI worsens with time[33,131] and that incidence of venous ulceration increases with age[132,133]. Based on the General Practice Research Database (GPRD), the estimated annual UK prevalence of venous ulceration is 1.7% in those over 65 years of age[133]. In the North American subfascial endoscopic perforator surgery (SEPS) registry, more patients with advanced CVI had primary venous insufficiency (70%) than had post-thrombotic syndrome (30%)[134]. The Bonn Vein Study[31] indicated that varicose veins may progress from a symptomatic or asymptomatic C2 class to higher clinical classes and CVI in a relevant percentage. In a study of 116 lower limbs of 90 patients who had at least two DUS scans before surgery (median interval period of 19 months), 31 legs (26.7%) were found to have ultrasonographic evidence of disease progression on the repeat scan[33]; thirteen legs (11.2%) also demonstrated clinical progression (7 from C2-C3; 4 from C3-C4; and 2 from C4-C6). In another study, 6% (3 of 50 limbs) of patients with initial C2-4 disease developed skin damage after 5 years; the rate of disease progression has been shown to be slower in primary than secondary CVD[135]. A 25-year population-based study reported the mean time for ulcers to develop from the time of the first CVD diagnosis is approximately 5 years[136].

There is reasonable evidence that the incidence, prevalence and characteristics of C4–6 disease may have changed considerably over the last 10–20 years and that further change is likely[137]. For example, given that there appears to be a clear relationship between age and the frequency of venous disease, increasing life-expectancy seems likely to increase the burden of C4–6 disease[110,136].

### Financial Cost

Annual health-care costs in the UK have doubled over the last decade to £126 billion[138], with a similar picture being seen in the USA and Europe[139]. The current global financial climate has naturally resulted in austerity measures, with the UK National Health Service (NHS) being no exception; it is required to make a 16% saving (£20 billion), whilst providing increasingly expensive investigative and therapeutic modalities and providing care for an increasingly demanding and aging population.

Varicose veins and venous ulcers can be a great financial burden to individual patients,

healthcare systems and to society as a whole. The symptoms associated with SVI and its complications may lead to loss of working days, prolonged sick leave and early retirement. The number of lost working days due to venous ulceration alone has been calculated at 2 million and 6.4 million days per annum in the USA[140] and France[141] respectively.

The direct medical cost of CVD in the USA has been estimated to be between $150 million and $1 billion annually; in the United Kingdom, 2% of the annual NHS budget is spent on the management of leg ulcers alone[100]. A study from France, reported in 1994[141], showed a total annual expenditure of €2.24 billion on CVD (2.6% of the national health budget); 50% of the costs were for varicose veins alone. Similar expenditure has been shown in other western countries[142,143]. Venous ulcers exhibit a chronic, relapsing and remitting nature, with patients often cycling between C6 and C5 disease, further adding to treatment costs. It would therefore seem prudent to find cost-effective treatments of uncomplicated SVI that can be implemented prior to more costly complicated disease developing, in addition to limiting the costs of C5/6 disease states.

### *Quality of Life Impairment*

The World Health Organisation defined "health" in 1948 as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[144]. Historically, assessment of a patient's health has been highly subjective, based on oral communication during consultation with a doctor. Subsequently, a number of health surveys were developed, but were largely non-validated and extremely time-consuming for patients and healthcare professionals alike. Over the last two to three decades, advances in psychometric analysis and clinical decision theory have facilitated the construction of validated scientific tools to provide a more objective measure of the impact of a particular disease process or condition on an individual patient level; the so-called "Health-related Quality of Life" (QoL). These tools, or "instruments", broadly fall into one of two categories: "Generic" or "Disease-specific". For a QoL instrument to be valuable, it must be practical (easy to administer), reliable (reproducible), valid (tests what it intends to test) and responsive (sensitive enough to identify small but important differences)[145]. (See Measuring Quality of Life in SVI, p.49, for a discussion of the QoL instruments typically used in SVI).

It is recommended that both generic and disease-specific instruments be used to assess QoL in patients with CVD, before and after treatment[146]; indeed it has been compulsory for all NHS providers of venous surgery (also surgery for groin herniae and unilateral hip and knee surgery) to measure QoL before and after interventions, since April 2009, as part of the PROMs (Patient Reported Outcome Measures) programme[147].

QoL has been shown to significantly deteriorate with the presence of SVI symptoms; the more significant the symptoms and severity of disease, the more profound the impairment in patients' QoL[148]. In a recent study from the Academic Vascular Surgical Unit in Hull[149], 456 patients with C2–C6 SVI were compared with control data for 105 people with C0–C1 disease. Increasing CEAP clinical grade corresponded strongly with the deterioration in disease-specific QoL (AVVQ), physical domains of the SF36, and in the EQ5D. Perhaps more importantly, this study also showed that there was no appreciable difference in the deterioration of disease-specific QoL between C2, C3 and C4 disease. Moreover, patients with symptomatic C2-6 disease can have SF36 bodily pain scores comparable to those of patients with recent acute myocardial infarction, while patients with C6 disease can suffer physical function and role limitation comparable to congestive cardiac failure or chronic obstructive pulmonary disease[150]. Another study[151] additionally showed that haemodynamic outcomes were not well correlated with QoL. Furthermore, it is well established that general practitioners underestimate patients' QoL deterioration in CVD[152].

These findings lead to the conclusion that patients cannot be selected for venous intervention based solely upon clinician-based assessments, but the decision must take into account the patient-reported symptoms and their consequent impairment of QoL. Whether QoL measurement alone can be used for rationing of venous intervention is another debate outwith the scope of this thesis.

At the commencement of this MD, the existing National Institute for Health and Care Excellence (NICE) guidelines[153] recommended that treatment be considered for varicose veins that impact on QoL, irrespective of the coexistence of complications. Hence, QoL assessment should be among the primary outcomes for any study on treatment of venous insufficiency; it must therefore be studied in detail. Information on the value of the health states associated with venous disease is also essential for economic evaluation in the context of health technology assessment.

Economic evaluation is becoming an increasingly common method by which health resources may be allocated in health care systems that are progressively suffering budgetary constraints. The agency tasked with this undertaking in the UK NHS is NICE. Quality Adjusted Life Years (QALYs) are becoming widely used as the basis of this cost effectiveness analysis assessing treatment effectiveness in units that are comparable across different interventions and diseases. There are two commonly used instruments that can create values upon which QALYs are calculated for any given health condition or treatment. These include the EuroQoL 5 domain (EQ5D) and Short-form 6 dimension (SF6D) generic QoL instruments (see Measuring Quality of Life in SVI, p.49 and Measuring Cost-effectiveness of Intervention for SVI, p.54).

## Aetiology & Risk Factors

Following on from the difficulties in precise epidemiological study, the risk factors associated with SVI and CVD in general have been difficult to establish. Aetiology across the disease spectrum appears multifactorial, with a complex interplay between the contribution of genetic and environmental components. Furthermore, much of the epidemiological evidence seems at odds with the pathophysiological mechanisms discussed earlier. Studies of potential risk factors and associations are epidemiological by their very nature, and therefore subject to the same criticisms and limitations as highlighted above.

SVI does appear to be more prevalent in females, as shown in the large-scale San Diego[154] and Framingham[121] cross-sectional studies, in addition to numerous other reports from London[155], Jerusalem[126], Finland[156] and Italy[157]. Explanations for this higher prevalence in females have suggested a hormonal effect on venous tone; both oestrogen and progesterone receptors have been identified in saphenous vein[158,159]. In keeping with this finding, pregnancy is known to result in an increase in GSV diameter[160], up to 25% for normal GSV, and 40% for refluxing GSV[161]; the calf-muscle pump[162] also has reduced efficacy. During the postpartum period, however, these veins return to their baseline sizes. It is less clear whether pregnancy simply accelerates the development of SVI in otherwise susceptible women[163], or whether it is an independent risk factor. Whilst some studies suggest that the prevalence of SVI increases with each pregnancy, others[164] have failed to show any difference.

Many of the large epidemiological studies mentioned earlier give conflicting information on potential associations between SVI and lifestyle influences such as smoking, alcohol intake and other dietary factors.

Only a few studies have examined the effects of alcohol consumption, which has been implicated as a risk factor in so many other disease processes. Early studies suggested alcohol was not a significant risk factor for varicose veins[120,165]. However, the methodology used (self-reporting) is known to underestimate levels of consumption. Later studies from Finland have indicated that the magnitude of alcohol consumption is correlated with SVI prevalence[166]. In large cross-sectional studies from Framingham[121], France[31] and Boston[165], SVI was more common in male smokers than male non-smokers. Conversely, similar studies from Germany[167] and Finland[156] indicated that smoking conferred a protective effect against varicose veins.

It has long since been proposed that a diet deficient in fibre, its consequent constipation and raised intra-abdominal pressure due to straining at stool are risk factors for varicose veins[168,169]. Raised intra-abdominal pressure is also considered as a possible alternative, or adjuvant, risk factor for the development of SVI in pregnancy. Furthermore, there has long been a belief amongst vascular surgeons that excessive BMI is associated with SVI, although its links are rather elusive[170].

However, in a detailed multivariate analysis of fibre intake, straining at stool and defecation frequency, these associations with SVI were not supported in the Edinburgh Vein Study[171], although there was a significant association between straining to commence the passage of stool and prevalence of moderate to severe truncal varicosities, but only in men. Another study found no association in either sex between the quantity of bread consumption and prevalence of varicose veins[166]. Furthermore, increased meat consumption, which has been used as a surrogate for poor dietary fibre intake, has been shown as protective against SVI in some studies[166].

Ultimately, it would appear that measures taken to modify environmental and lifestyle influences are unlikely to either prevent SVI or arrest its progression. Hence the treatments discussed later (see 1.4 Treatment of SVI, p.55) would appear to have more scope in alleviating or at least limiting the impact of the disease.

## 1.3 Assessment of SVI

### History & Examination

The majority of patients with signs of SVI who present to their general practitioner and are ultimately referred on for a specialist vascular opinion have significant symptoms as outlined earlier. Some will additionally have a history of complications such as superficial thrombophlebitis or bleeding from varicosities. Less frequently, the veins are of cosmetic concern only[100]. However, there is of course a degree of overlap between the common symptoms of SVI/CVD and other conditions of the lower limb, or even the wider cardiovascular system. It is therefore of paramount importance to obtain a thorough clinical history and perform clinical examination in order to conclusively attribute the patients' symptomatology to any detected underlying venous insufficiency and ensure that other serious conditions are not overlooked.

Clinical examination should be undertaken with the patient standing in a warm, well-lit room. Inspection and palpation are the key aspects of examination, aiming to identify any of the classical features of CVD (see Clinical Presentation and Classification, p.30) and their location. As outlined earlier, the clinical assessment of patients with SVI should include classification with the CEAP and VCSS at baseline and again after any intervention.

Examination of patients presenting with signs or symptoms consistent with CVD has classically involved performing supplementary techniques such as the tourniquet (Brodie-Trendelenberg), cough impulse and tap tests in clinic to try and distinguish deep from superficial venous reflux. The Brodie-Trendelenberg test is performed with the patient initially lying supine to empty the lower limb veins. After applying either tourniquets or manual compression at varying levels, the patient is asked to stand. In the presence of SVI the varicose veins will remain collapsed if compression is more proximal than the point of reflux. With deep (or mixed) venous insufficiency, the varicose veins will appear despite the use of the tourniquet or manual compression.

These clinical examination techniques do not help determine the extent or severity of disease or provide information about the cause[2]. They have been shown to have poor sensitivity and specificity in localising sites of reflux (0.15 and 0.91; 0.67 and 0.59; and 0.924 and 0.18 for Brodie-Trendelenberg, cough and tap tests, respectively)[172].

Additionally, it is shown that the external site of varicosities is a poor predictor of the underlying truncal system involvement[30].

In a survey of vascular surgical examiners of the Royal College of Surgeons of England and basic surgical trainees, the general consensus was that these examination techniques were outdated[173]; a preference for hand-held doppler examination was found.

### Continuous-wave Hand Held Doppler

The use of continuous wave hand-held doppler (HHD) was first introduced to outpatient venous assessment in the early 1990s[174], and has often been used to assist in clinical evaluation by determining the presence and direction of flow in the veins. At each venous location, with the patient standing, the presence of a spontaneous (unaugmented) forward doppler signal is documented. Venous incompetence is detected by demonstrating flow reversal; a Valsalva manoeuver is often sufficient to diagnose DVI in the CFV, whereas distal augmentation manoeuvers (calf squeeze and release) are usually required to detect SVI due to the lower flow velocities.

Compared with the poor accuracy of the traditional clinical examination techniques, HHD has been shown to have respective sensitivity and specificity of 0.92 and 0.94 for detecting reflux at the SFJ[172]. A previous study also showed HHD correctly identified GSV and SPJ reflux in 91% and 71% of cases respectively. A limitation of the HHD examination relates to the inability to confidently and exclusively insonate individual vessels; flow is detected in any vessel within the path of the ultrasound beam. The lack of direct visualisation of the vessels creates uncertainty about the precise site of reflux[2]. This is further limited in the popliteal fossa due to the more complex anatomical arrangements; in a comparative study with DUS, HHD had only 44% sensitivity at the SPJ.

Given the anatomical and pathophysiological factors discussed earlier, it is not surprising that both traditional examination techniques and HHD have been shown to be unreliable[175]; this is highlighted even further in the current era of image-guided endovenous treatments.

What is clear, then, is that while HHD is superior to traditional clinical examination techniques in identifying reflux, it is not sufficiently accurate to be used as the exclusive investigative modality.

## Anatomical imaging and haemodynamic assessment

### Duplex Ultrasonography

Venous duplex ultrasonography (DUS) combines anatomical and morphological B-mode ultrasound imaging with pulse-wave doppler assessment of blood flow. This provides information on both the anatomical arrangement and extent of disease involving the deep, superficial and perforating vessels; addition of colour doppler makes it easier to visualise obstruction, turbulence, and the direction of venous and arterial flow[111, 176]. As such, DUS scanning overcomes many of the limitations of HHD examinations, and has significantly higher diagnostic accuracy[177]. Other parameters such as the reflux velocity and even the reflux volume have been used to assess the severity of reflux[178], although these are not commonly used in routine practice. In the context of DVT, DUS is also able to differentiate between acute and chronic changes[179].

DUS is recognized as the "gold standard" investigation and is recommended as the first diagnostic test for all patients with suspected CVD[100,180-182], supported by strong evidence concerning safety and noninvasiveness, cost-effectiveness and reliability. A clinical trial from Sweden prospectively randomized 343 legs with varicose veins to either undergo preoperative DUS (166 legs) or no preoperative imaging (177 legs) prior to scheduled surgery. The preoperative DUS group demonstrated significantly lower recurrence rates at both two[183] and 10[184] years following surgery.

International consensus has standardized many aspects of the DUS examination technique, the definitions to be used in diagnosing insufficiency and the standards in reporting the examination. Significant reflux is defined as 0.5 seconds or greater in the superficial venous system; 1.0 seconds or greater for the deep system. In addition to consensus surrounding the use of preoperative DUS, it is also a mandatory aspect of planning, performing and follow-up of endovenous treatments for SVI[185]. Recommended reporting standards and outcome assessment for endovenous ablation

have recently been published in a joint statement of the American Venous Forum and the Society of Interventional Radiology[146,186].

As detailed earlier, DUS imaging has enabled in-depth studies of the patterns of reflux seen in patients with SVI. Additionally, it has been shown that the extent of reflux shows a positive correlation with both the magnitude of venous hypertension and increasing clinical severity[31,32,187]; both the length of incompetent vein[22] and its diameter[188] show a similar association with clinical severity. The introduction of DUS also provides *in vivo* knowledge of venous hemodynamics. It also allows mapping of the haemodynamics of the venous system, providing precise information on any changes or abnormalities[33,180,181].

Whilst DUS alone is sufficient as the sole investigative modality for the overwhelming majority of patients with SVI, it does have limitations. DUS is an operator-dependent examination; the user is relied upon to have an in-depth knowledge of the venous anatomy, potential variations and implications for treatment. In complex cases, it is a time-consuming procedure, with potential for omission of perforators in unusual locations and difficulty in the evaluation of pelvic vessels[189]. Furthermore, it is often difficult to gain suitably accurate images proximal to the inguinal ligament, particularly in overweight patients.

Specific aspects of DUS relevant to individual treatment modalities will be discussed in the appropriate sections later. A standard venous DUS examination is performed to identify sites of junctional incompetence and reflux in superficial axial veins and exclude obstruction or thrombus in deep veins, using venous compressibility and assessment of flow.

### Plethysmography

Plethysmography (air-, strain-gauge- or digital-photo-) is an indirect, non-invasive technique for the assessment of calf muscle pump function, venous reflux, and venous outflow obstruction. It consists of exercise venous plethysmography, measurement of passive refill and drainage, and outflow plethysmography. Plethysmography quantifies venous reflux and obstruction and has been used to monitor venous functional changes and assess physiological outcome of surgical treatments[190].

The use of plethysmography is not typically indicated in the vast majority of patients with uncomplicated SVI, but it may be used as a supplementary examination in patients with suspected outflow obstruction or calf muscle pump dysfunction in the absence of DUS findings. The American Venous Forum guidelines suggest the use of air plethysmography is "best practice" in the evaluation of patients with advanced CVD (CEAP classes C3-6) if DUS does not provide a definitive diagnosis[100].

### *Venography*

#### Invasive Contrast Venography

Ascending or descending contrast venography is performed selectively in patients with complex disease, typically those with deep venous obstruction, post- thrombotic syndrome or supra-inguinal diseases such as May-Thurner syndrome, Nutcracker syndrome, gonadal vein incompetence or pelvic congestion syndromes and complex arteriovenous malformations. Direct catheter-venous pressure measurements may additionally be used in these situations. Since the advent of cross-sectional venographic modalities (CT and MRI), invasive contrast venography is usually reserved for endovenous or hybrid deep venous procedures such as thrombolysis, angioplasty and venous stenting or venous reconstructions.

#### MRI/CT Venography

The techniques of computed tomography and magnetic resonance imaging have progressed significantly in the past decade, and they provide excellent three-dimensional imaging of the venous system and have largely superseded the invasive contrast techniques outlined above. They provide a detailed, but static evaluation of anatomy, and do not give haemodynamic information. Additional possible disadvantages include renal dysfunction and allergic reaction to radiocontrast, and expense[189].

## Measuring Quality of Life in SVI

As outlined earlier (see Quality of Life Impairment, p.41), SVI has a significant impact on QoL. Since the vast majority of patients will not die from the disease, the focus for treatment should be on improvement in, or at least preventing further deterioration of,

QoL. International consensus states that measurement of QoL in SVI should be undertaken using both generic and disease-specific instruments[146].

### *Generic QoL instruments*

Generic instruments assess global states of well-being across a wide variety of conditions and diseases and provide a measure of treatment efficacy. They have high comparative value for unrelated conditions and are generalisable between studies. These instruments help establish the relative priority of a procedure, and can be used to calculate cost-effectiveness, which is becoming increasingly important in the current era of strained finances and resources.

### The 36-Item Short Form Health Survey (SF36)

The 36-item Short Form Health Survey (SF36) (QualityMetric, Lincoln, RI, USA) was designed to replace the aforementioned time-consuming health surveys and was developed from the Medical Outcomes Study[191] and the RAND health insurance study[192]. The instrument comprises measures of physical, social and psychological well-being, broken down into eight "domains": -

- Physical functioning
- Role limitation due to physical problems (role-physical)
- Bodily pain
- General health perception
- Vitality
- Social functioning
- Role limitation due to emotional problems (role-emotional)
- Mental health

Individual scores from 36 questions are numerically coded and transformed into a scale from 0 (worst health), to 100 (best health) for each domain. This tool is the most widely used generic QoL instrument[193], shown to be valid and reliable[194-198] in many patient groups and diseases, including venous insufficiency[198,199]. The SF36 QoL domains have been compared with numerous other health-related dimensions, including ability to work, symptom severity, use of healthcare resources and also mental health criteria; the associations have been shown to be significant and

consistent[200]. The SF36 is now in its second version, in which some of the question response options have been amended to improve respondent understanding.

### The EuroQoL 5-Domain Instrument (EQ5D)

The EQ5D™ 3-level instrument (EuroQol Group, Rotterdam, The Netherlands) was introduced in 1990[201] to provide a simple, generic measure of health for both clinical and economic appraisal. It is applicable to a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue score (VAS). The descriptive system comprises five domains:-

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

Each domain has three levels:

1. No problems
2. Some problems
3. Extreme problems

Respondents are asked to indicate their health state by marking the most appropriate response level in each of the five domains. Each individual completed instrument thus has a 5-digit code referring to that respondent's health state, for example 11111 would equate to no problems in any of the five domains; 33333 indicates extreme problems in all five domains. This gives a total possible 243 health states ($3^5$).

The VAS records the respondent's self-rated health on a vertical "thermometer" from 0, or "worst imaginable health state" to 100, or "best imaginable health state".

The five-digit descriptive system can be converted into a single summary index, or "utility index score," by applying a formula that attaches weights to each level score within each domain. The UK weights were derived using "Time Trade Off" (TTO) responses from 3395 adults in the general population[202]. In the TTO task, respondents

are asked, for example, to imagine they live in a health state (e.g. 21212) for 10 years and then asked to specify the amount of time they are willing to give up to live in full health (i.e. 11111) instead. Statistical modelling of the TTO responses has given rise to a linear scale of values, where 1 = full health and 0 = death. The minimum value on the scale is -0.594; values below 0 are considered to represent a health-state worse than death.

The EQ5D has been shown to be valid[201,203,204] and is a popular system worldwide, available in 150 languages with population weightings calculated for 15 countries. It has attracted some criticism in terms of having poor sensitivity to detect improvements in conditions that have low morbidity[205], and is better able to detect large differences in health than small ones. To address these criticisms over sensitivity, a task force of the EuroQoL group decided in 2005 that each of the five domains should be given five levels of severity; the so called EQ5D-5L. The 5-level system has been validated, but as yet no population weightings have been developed.

### *Disease-specific QoL instruments*

Disease-specific instruments focus on the domains most relevant to the disease or condition under study and on the characteristics of patients in whom the condition is most prevalent[145]; therefore sensitivity to small but clinically significant outcomes within the specific condition is increased. The questions within disease-specific instruments are typically familiar to the target population, and therefore more acceptable than generic instruments.

### The Aberdeen Varicose Vein Questionnaire (AVVQ)

The AVVQ was first disseminated for use in 1993[198] and consists of 15 questions directly related to venous disease, both physical and social. It has been validated with those undergoing venous surgery and is reported to take approximately 5 minutes to complete[206]. The first question asks the respondent to draw their varicose veins onto a diagram of the legs; the assessor subsequently overlays an acetate with a grid pattern, and the number of boxes involved by varicose veins on each leg are counted. The following 14 questions use Likert-type scales of between two and four possible response options, with a time frame of the preceding 2 weeks. The responses are computed to generate a single overall score on a scale between 0 (no features or

evidence of venous disease) and 100 (the most severe features of venous disease, affecting both legs).

The AVVQ was developed after a clinical literature review, consultation of an expert panel and patient focus group, with subsequent testing and validation in patient samples and the general population. It has been shown to have strong reliability and validity[198,199,206], and correlates well with both patient-reported symptom questionnaires and the SF36; in particular the physical functioning, role-physical, bodily pain and social functioning domains[206].

Use of the AVVQ has been well established in a large number of venous intervention studies, and it is a very familiar tool for UK-based vascular surgeons. Hence, it was selected as the disease-specific QoL instrument in the NHS PROMs programme.

Within CVD, there are a small number of other disease-specific QoL tools; none have gained general acceptance, possibly because none is entirely satisfactory for application to the full spectrum of CVD[111]. Their respective utility and limitations are highlighted below.

## VEnous INsufficiency Epidemiologic and Economic Study of Quality of Life/Symptoms (VEINES-QOL/Sym) questionnaire

VEINES-QOL/Sym[207] measures the impact of CVD on symptoms and QoL from the patient's perspective using 26 questions, developed from a study of 1531 CVD patients in Belgium, France, Italy, and Canada. From the questionnaire responses, separate summary scores for both QoL and symptom severity are calculated; higher scores indicate better outcomes. The time frame for the instrument is the preceding 4 weeks, as in the SF36. It has been shown as reliable, valid and responsive to change[148,207,208], but has been used little in studies performed by investigators outside of its original developers[111].

VEINES-QOL/Sym was shortlisted along with the AVVQ for use in the NHS PROMs programme, but ultimately lost out due to its lesser familiarity to practicing UK vascular surgeons[209].

### Chronic Venous Insufficiency Questionnaire (CIVIQ)

The CIVIQ[210] is a short 20-item questionnaire developed to measure physical, social, psychological and pain domains; the instrument has recently been revised (CIVIQ 2)[211]. It has good reliability and validity[206], but the four domains it assesses are more focused on the less severe end of the disease spectrum and it includes some non-specific end points, such as symptoms of heavy legs, paraesthesia, burning and nocturnal cramps.

### Charing Cross Venous Ulcer Questionnaire (CXVUQ)

The CXVUQ[212] is an instrument for measuring QoL in patients with venous ulcer disease. It provides a consistent measure of patient-reported QOL in venous ulcers regardless of the treatment selected. Combining it with a generic measurement instrument may provide valuable information on the progression of ulcers and on the available treatment measures, although clearly it is unsuitable for assessing patients with C2-C4 disease.

## Measuring Cost-effectiveness of Intervention for SVI

In addition to simply assessing any improvement in QoL, the values gained can be used to calculate cost-effectiveness. As highlighted earlier, SVI is a significant burden on the cost to individual sufferers, society and in particular the healthcare system. Since 2009, the NHS contract for provision of acute services has mandated that all providers of venous intervention should take part in the PROMs programme. Part of this programme is to provide data that can be used in subsequent cost-effectiveness calculations.

The EQ5D (3-level), using the TTO technique, is the recommended measure on which to base cost utility analyses in the UK[213]. In the background work looking at potential instruments to be used in the NHS PROMs programme[209], the EQ5D met all the operational criteria. Additionally it is endorsed by NICE, which requires that *"...health states should be measured in patients using a generic and validated classification system for which reliable UK population preference values, elicited using a choice-based method such as the time trade-off..."*[213]. Conventional techniques for valuing health states such as TTO have been criticized for being too complex in vulnerable patient groups and that the values generated may be distorted.

However, there has been some more recent testing of the SF6D, a single utility index that represents the QALY, which can be derived from SF36 data[205,214]. SF6D values were derived from the standard gamble (SG) technique; in this method of QALY derivation, patient utility is ascertained under the conditions of choice and uncertainty[215]. The SF6D may have two main advantages in that it is thought to be more responsive than the EQ5D and may allow retrospective assimilation of data from studies that have previously reported SF36 outcomes.

Studies of intervention for SVI that report both EQ5D and SF36 data in addition to a validated disease-specific QoL instrument should therefore be considered optimal.

## 1.4 Treatment of SVI

### 1.4.1 Compression

Compression therapy is classically the most basic and frequently used treatment for the full spectrum of SVI; it is often referred to as "conservative" treatment, in conjunction with lifestyle modifications such as weight loss, exercise, elevation of the legs when sitting and avoidance of prolonged standing. Whilst these additional "conservative" measures appear to make sense on a physiological level, there is no scientific evidence to show they have any bearing on symptoms, disease progression, or QoL.

The underlying mechanism of compression is to decrease ambulatory venous hypertension. Radial compression pressures required to occlude the superficial leg veins in the supine position range from 20 to 25mmHg. In the upright position, pressures of 35 to 40mmHg result in narrowing of the superficial veins, while pressures over 60mmHg are needed to fully occlude them[216].

Compression therapy can be delivered by an almost overwhelming number of methods, which include graduated elasticated compression stockings, single or multilayer elastic or non-elastic bandaging systems, dressings, non-elastic garments, paste gauze boots (Unna boot) and pneumatic compression devices. The degree of compression, modality chosen and duration of therapy is dictated predominantly by the severity of disease being treated, although the evidence is not entirely clear-cut in each

case, and further patient and physician preferences have an additional role in the ultimate choice of therapy.

In the UK NHS, the typical choices of compression are either graduated elasticated compression hosiery (stockings), or a bandaging system. Stockings are classified by the degree of radial pressure exerted at the ankle; the degree of compression gradually reduces from distal to proximal in order to promote normal cephalad flow of venous blood. Two systems of classification are in common use in the NHS; the British Standard (UK) system and the RAL (German) system (Table 7): -

| Class | Compression at ankle (mmHg) |
|---|---|
| UK Class 1 | 14 – 17 |
| UK Class 2 | 18 – 24 |
| UK Class 3 | 25 – 35 |
|  |  |
| RAL Class 1 | 18 - 21 |
| RAL Class 2 | 23 - 32 |
| RAL Class 3 | 34 - 46 |

**Table 7: Classification of graduated compression hosiery**

In addition to the above disparity between the two systems in terms of the degree of compression exerted, the RAL stockings are quality assured to maintain their certified compression for up to 6 months, whereas the British Standard stockings should be replaced every three months (based on daily wear). Furthermore, there is plethysmographic evidence to suggest that some aspects of SVI, such as oedema, fare better with a stiffer stocking[217]; there is currently no consensus on the degree of stiffness, nor on the amount and degree of pressure graduation from the ankle to the calf[20]. Compression stockings used for SVI are typically below-knee length, although full-length stockings are also used.

The evidence for compression therapy in specific grades of SVI is discussed below.

*Uncomplicated Varicose veins (CEAP C2)*

Overall, there is a paucity of good-quality evidence for compression as the primary treatment of uncomplicated SVI. Additionally, many studies were conducted before the current established consensus on clinical classification and terminology; a recent Cochrane systematic review of compression stockings in C2-4 disease[218] identified seven eligible RCTs, of which none used the CEAP classification. Overall, there was considerable heterogeneity between the studies, both in terms of participant characteristics and the class of compression used. The authors were unable to draw any firm conclusions on the value of compression stockings as the primary or initial treatment in C2-4 disease.

Reported case series of patients treated with compression stockings also frequently include the whole spectrum of disease from C1-6, making extrapolation of results difficult. In a study of 112 patients with C2-6 disease, treatment with 30 to 40mmHg compression resulted in significant improvements in pain, swelling, pigmentation, activity and well-being at 16 months after initiation of therapy, with overall compliance of 70%[219]. Such high levels of patient compliance are unusual, even more so with high compression. In a study of 3144 patients with the full spectrum of CVD (primary and post-thrombotic) referred to a secondary care vascular service, only 21% were fully compliant with prescribed compression therapy. There were no differences in non-compliance rates between different CEAP classes or age groups[220].

In the NHS-funded REACTIV study, the efficacy of conservative management of patients with varicose veins was compared with conventional surgery and sclerotherapy. Patients were categorised into one of the three following groups:

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

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

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

Within each group, patients were randomized to one of two specific therapies: -

- Group 1:
    - Conservative treatment or
    - Sclerotherapy (see 1.4.4 Sclerotherapy, p.76);
- Group 2:
    - Conventional surgery (see 1.4.3 Conventional Surgery, p.64) or
    - Sclerotherapy
- Group 3:
    - Conservative treatment or
    - Conventional surgery.

At one year, 57% of patients randomized to conservative management (Groups 1 and 3) expressed significant discontent with their treatment; 50% requested intervention. By three years, 51.6% of patients allocated to receive conservative therapy in Group 3 had opted to cross into the surgical arm. The surgical arm of Group 3 demonstrated significantly improved QoL, symptomatic relief, anatomical improvement and patient satisfaction. Careful follow-up logs were kept of patients who declined randomization within each group; among the 290 patients classed as Group 3 who declined to participate, 198 (68%) had undergone varicose vein surgery within 12 months of follow-up[221]. Conservative management was also calculated as the least cost-effective of the three treatment strategies (see sections on Sclerotherapy, p.76 and Surgery, p.64 for further discussion).

The level of compression for patients with C2 disease is also disputed. A meta-analysis of 11 RCTs[222] found that in healthy patients with C1-3 disease, and in patients after varicose vein surgery, Class 2 stockings may not offer any additional benefits over Class 1. Evidence suggests that lower compression classes are better tolerated[223], thus compliance is likely to be higher and therefore any clinical benefit more likely to be seen.

Whilst compression therapy may be considered "conservative", this does not equate with "inexpensive" nor "easy". In a recent study of 16,770 patients with CVD in Poland[224], 33% of patients who discontinued wearing their prescribed compression stockings cited expense as the reason for doing so. Other reasons were sweating (27.3%), itching (13.6%), cosmesis (13.6%), oedema (6.8%), exudate (3.4%) and difficulties with application (2.3%). Furthermore, some patients, particularly those who are elderly or who have physical, mental or visual impairment may have greater difficulties applying stockings. One study of predominantly elderly women with CVD found that 15% could not apply elasticated stockings and 26% needed considerable help to do so[225]. Compression should only be prescribed and applied by professionals with the necessary skills and training[100]; inadequately prescribed, measured or fitted stockings may precipitate cases of skin breakdown or necrosis[226].

The need for a period of compression treatment before any intervention for simple varicose veins has been surrounded by controversy. Although third-party payers often require a trial of compression stockings, there is virtually no scientific evidence to support such a policy when saphenous ablation to treat superficial reflux is both more efficacious and cost-effective, as supported by the REACTIV trial data[221].

A recent systematic review of compression in C2 disease[227] analysed data from 11 level 1 studies, 12 nonrandomized studies, and 2 guidelines. The authors reported a poor quality evidence base for the use of compression in this patient group and could not support its use. In common with real-life experience in clinical practice, poor compliance with compression treatment may have attenuated any positive effects. Whilst there is evidence supporting an improvement in symptoms, with maximal relief from Class 2-3 (25-35 mmHg) compression[100], there is no convincing evidence that compression has any effect upon disease progression, or in preventing recurrence after surgical intervention.

There has been a paradigm shift in the use of compression over recent years; the latest guidelines from both NICE[228] and the Society for Vascular Surgery/American Venous Forum[100] suggest not providing compression as the sole treatment for SVI in patients who are suitable for intervention. It is not long, however, since studies suggested that it could be used as a stand-alone treatment[222]; unfortunately this still appears to be the case at a primary care level, with referral criteria for general practitioners commonly

requiring a defined period of conservative management before secondary care referral will be considered[229]. Based on the above evidence, in disease short of ulceration, those patients may be being put at considerable disadvantage. Where compression may be of benefit in uncomplicated disease, however, is in patients in whom there is doubt over the aetiology of symptoms, or who report atypical symptoms; patients whose symptoms improve after compression therapy are reportedly over 15 times more likely to have an improvement in their symptoms at 1 month (RR [95% CI] 15.6 [4.3-56.5]), and 21 times higher at 1 year after surgery (21.3 [4.7-96.9]), compared with those who had no improvement with compression[230].

### CEAP classes C3-6

The evidence for compression therapy as primary treatment in more advanced SVI is somewhat more convincing than for uncomplicated disease. Compression therapy improves calf muscle pump function and decreases reflux in vein segments in patients with CVI[231,232].

#### Compression versus No Compression

A cohort study of 113 patients with venous ulcers, treated over 15 years, identified that graduated compression is effective as the primary treatment to aid healing of venous ulceration and as adjuvant therapy to interventions to prevent recurrence of venous ulcers[233]. It also identified that compliance with compression therapy is a key issue, as has also been alluded to in uncomplicated disease. Ulcer healing rates were 97% and 55% in compliant and noncompliant patients respectively (p<0.0001); ulcer recurrence was 16% in compliant patients and 100% in noncompliant patients. A systematic review of 24 RCTs on compression treatment on venous ulcers[234] concluded that compression treatment improves the healing of ulcers compared with no compression and that high compression is more effective than low compression.

#### Compression stockings versus bandages

A 2009 meta-analysis[235] of 692 patients from eight RCTs comparing compression stockings with bandages showed faster ulcer healing with stockings than with bandages (*p*=0.0002). Three of these studies also examined pain, which was

significantly less with stockings than with bandages (p<0.0001). Another systematic review by Partsch et al[236] confirmed that compression bandaging promotes healing of venous ulcers and that Class 3 stockings are superior to lower classes. Class 3 compression stockings also prevent recurrence of ulceration after healing. A recent evidence summary on ulcer disease[237] supported these recommendations. There is currently not enough rigorous evidence to determine whether Class 3 stockings or the classic four-layer bandaging are superior in healing venous ulceration. The recently published RCT of 2-layer compression hosiery versus four-layer compression bandaging (VenUS IV)[238] showed equivalent healing rates (HR 0.99, 95% CI 0.79-1.25, p=0.096), with median time to healing 99 and 98 days respectively. However, a considerable 38% of hosiery patients changed treatment (presumably to bandaging) during the study, and the number of patients receiving surgical intervention was not reported.

### Compression versus Surgery or venous ablation

A systematic review[239] identified two RCTs of open venous surgery on C6 patients. The first trial[240] compared open surgery on the superficial and perforator veins along with compression treatment with compression alone in 200 legs (170 patients) with active venous ulceration. After 24 months of follow-up there was no statistically significant difference in ulcer healing between the two arms (83% compared with 73% [p value not reported]). However, over a mean follow-up period of 29 months the ulcer-free rate in the surgery/compression arm was 72% compared to 53% (mean follow-up 26 months) in the compression only arm, although this difference was not statistically significant (p=0.11).

The second, more robust, Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) trial[241,242] randomised 500 participants with active or recently healed ulcers to receive either superficial venous surgery and compression treatment or compression alone. The trial reported no statistically significant difference in ulcer healing rates between participants allocated to open surgery and compression compared with compression alone at 24 weeks follow-up (65% for both groups, p=0.85). However a statistically significant reduction in ulcer recurrence at 12 months was seen in the open surgery/compression arm compared to compression therapy only

(12% versus 28% p<0.001). This difference in recurrence was even greater after four years[243] (for further discussion of the ESCHAR trial, see Surgery, p.64).

In addition to compression, further specialized dressings are commonly used in order to provide additional wound healing benefits. A Cochrane systematic review of 42 RCTs[244] searched for evidence of effectiveness of dressings applied to venous leg ulcers in addition to compression. This concluded that there is no evidence to recommend the addition of extra dressings (e.g. hydrocolloids) over compression alone

## 1.4.2 Pharmacological

Pharmacological treatments for venous insufficiency have been available for many years, but have yet to make it into the mainstream treatment armamentarium of most vascular surgeons. A vast array of substances have been used with varying success, but the most promising are "venoactive" drugs, including naturally-derived (plant-extract) products such as horse chestnut seed extract (aescin), flavonoids, micronized purified flavonoid fraction (MPFF), and French Maritime Pine bark extract. Synthetic venoactive products include calcium dobesilate, naftazone, and benzarone.

The principle aim of venoactive drugs is to improve venous tone and capillary permeability, probably through noradrenergic pathways[245], although a precise mechanism of action for most of these drugs is unknown. Flavonoids appear to modify leucocyte activity and reduce endothelial inflammation and oedema[2].

A Cochrane systematic review of 44 studies[246] identified significant limitations in terms of heterogeneity in study populations, methodology, disease classification and outcome measures. Overall, the authors found a slight positive effect on oedema and on restless leg symptoms. However, it was concluded that there is insufficient evidence to support the global use of venoactive drugs in the treatment of CVD. A separate Cochrane review of 17 RCTs found that horse chestnut seed extract (aescin) was effective in decreasing oedema, pain, and itching in the context of CVI[247].

In addition to questionable efficacy in C2-4 disease, these substances are not entirely innocuous. A number of side effects and adverse events, primarily gastrointestinal, have been noted and agranulocytosis has also been reported[246-248].

In the context of venous ulceration, there is some modest evidence for pharmacological treatment in addition to compression therapy. A meta-analysis of five RCTs[249] that included 723 patients with C6 disease found a 32% increased chance of ulcer healing at six months in patients treated with compression plus adjunctive MPFF compared to those treated by compression therapy alone (relative risk reduction, 32%; 95% CI 0.03-0.70).

The phosphodiesterase inhibitor Pentoxifylline, more commonly used in intermittent claudication, also has some reported beneficial use in venous ulcer disease. In a double-blind, placebo-controlled trial, complete healing of venous ulcers was observed in 64% of patients receiving pentoxifylline and in 53% of the patients receiving placebo, although the difference was not statistically significant[250]. The beneficial effects of pentoxifylline appear greater at higher doses; Falanga *et al*[251] investigated the effect of pentoxifylline on ulcer healing in a RCT of 133 patients. Patients who were given 800mg three times daily (TDS) healed faster than those receiving placebo (p=0.043). The median time to complete healing was 100, 83, and 71 days for placebo, pentoxifylline (400mg), and pentoxifylline (800mg) TDS, respectively. However, the quicker healing time with the higher dose came at the expense of more significant gastrointestinal side-effects.

Overall, there is little evidence in the literature to encourage the routine use of pharmacological agents in SVI, particularly in the face of more efficacious invasive alternatives. Despite this, the cost of these drugs to healthcare systems is significant; in Germany in 1995, the expenditure on venoactive drugs exceeded that for chemotherapeutic agents[252]. Large-scale RCTs assessing the typical outcome measures in venous intervention, including QoL and cost-effectiveness, are yet to materialize.

## 1.4.3 Conventional Surgery

The surgical technique will be considered in some detail, as it remains the single most commonly performed procedure for SVI and is still regarded as the gold-standard procedure with which all newer techniques are compared. Many aspects and issues associated with the surgical technique are subsequently addressed by newer technology to be discussed later, hence it is important to put these aspects into context, within the following broad outcome categories:-

- Technical Success and Recurrence
- QoL
- Clinical outcomes and complications
- Variations in technique and technical modifications

The newer techniques will then be discussed in turn, using the best evidence available at the onset of this programme of research; the area is rapidly evolving and hence further pertinent studies that have come to light during this period will be discussed, where relevant, later in this thesis.

### *Surgical Procedure*

SFJ ligation, stripping of the GSV and avulsion of varicosities (so-called High-Tie, Strip and Avulsions; HTSA) is accepted as the gold-standard surgical procedure for patients with SVI attributable to SFJ and/or GSV reflux with associated varicose veins. It has evolved and developed as a procedure over the centuries, from initial reports by Ambroise Pare, and subsequent modifications by many of the great names in surgery such as Trendelenberg, Mayo, Babcock, and others. A similar, albeit slightly modified, technique is performed for SPJ and SSV reflux (see below).

Prior to surgery, the patient is consented and marked; any visible varicosities on the leg to be treated are marked with indelible ink whilst the patient is standing, to facilitate phlebectomy of these veins later.

The majority of patients in the UK undergo surgery under general anaesthesia (GA), with a smaller but significant number having spinal anaesthesia.

After preparing the leg with a suitable antiseptic solution and draping, an oblique skin-crease incision, 3-4cm in length is made 2cm inferior & lateral to the pubic tubercle in the groin. After dividing the cribriform fascia, the SFJ is carefully dissected to reveal all its tributaries and the anterior aspect of the CFV. The GSV is identified and disconnected, while all other SFJ and GSV tributaries are ligated and divided back to their secondary branches[99,253], the SFJ is then ligated and divided, taking care not to leave a significant redundant stump, but also not to impinge the CFV[100]. Any arterial structures in the vicinity of the SFJ, such as the external pudendal artery, are carefully preserved wherever possible.

Stripping of the GSV is facilitated by passing either a flexible or rigid PIN (Perforate INvaginate) stripper along the vein lumen to exit through a small incision at or just below knee-level. The GSV is tied to the proximal tip of the stripper, and the vein is inverted into its lumen as the stripper is pulled down through a small incision made below the knee. Several RCTs and large cohort studies have proven that failure to strip the GSV, at least to the level of the knee, is associated with an unacceptable incidence of recurrence[254-256] and sub-optimal results in terms of QoL and haemodynamic improvement[257]. GSV stripping below the knee is rarely performed today because of an increased incidence of reported saphenous nerve injury[258]. This may therefore leave a significant segment of GSV with residual reflux below the knee.

The operation is usually completed with phlebectomy (avulsion) of the premarked varicosities through small (2-3mm) stab incisions. At the conclusion of the operation, the groin incision is closed in layers with absorbable sutures; the phlebectomy incisions and stripper exit site are typically closed with sterile adhesive strips only. The leg is then dressed with absorbent gauze and bandaged with a crepe bandage. After a period of observation in a postoperative recovery area, most patients will be discharged home the same day, commonly with graduated compression stockings. Protocols for duration of post-operative compression therapy and further follow-up of these patients vary widely, largely due to surgeon preference, with little in the way of rigorous evidence.

Post-operative compression therapy is postulated to reduce haemorrhage, oedema, haematoma and pain, but a RCT of 220 patients undergoing conventional surgery found no benefit in compression for greater than one week with respect to

postoperative pain, number of complications, time off work or patient satisfaction for up to 12 weeks after surgery[259].

### Differences in technique for the SSV

Complete stripping of the SSV is rarely performed today due to higher than acceptable risk of injury to the sural nerve; ligation of the SSV through a small transverse incision in the popliteal crease can be performed together with a limited invagination stripping of the vein to the mid calf, using the PIN stripping technique described for the GSV earlier[100]. The safest technique to identify the SSV is intraoperative DUS scanning. There is no evidence that flush ligation is superior to simple ligation of the vein when performed at a location closer to the skin, usually in the knee crease. The American Venous Forum guidelines recommend ligation of the SSV at the level of the knee-crease, about 3 to 5 cm distal to the SPJ, since this can be performed through a very small skin incision and it avoids the need for deep dissection in the popliteal fossa, with the potential for associated wound complications or nerve injury.

### Phlebectomy

Phlebectomy was first described by Aurelius Cornelius Celsus (25 BCE-50 CE) and was reinvented around four decades ago by Robert Muller, a dermatologist in private practice in Switzerland[260]. The initial presentation of his new technique at the Congress of the French Society of Phlebology in 1967, was poorly received, yet he continued to refine the technique and his own surgical instruments; the technique of stab avulsion phlebectomy is now practiced worldwide by Vascular surgeons and "phlebologists". ''Mullerian ambulatory phlebectomy'' should be considered the gold standard for removal of superficial varicose veins; Muller is often referred to as the "father" of modern-day ambulatory phlebectomy. Phlebectomy can be carried out concomitantly (at the same procedure as high-tie and stripping), or as a delayed procedure sequentially.

### Outcomes of Surgery

#### Technical Success and Recurrence

Results of conventional surgery have continued to improve over the past decades; HTSA of the GSV undertaken as a daycase operation is safe and effective. Recurrence

of varicose veins after conventional surgery is a common problem, with increasing prevalence over additional years of follow-up. Reported rates in the literature are as high as 30% at 1 year, 40% at 2 years and up to 66% beyond 10 years[58,255,261-264]; recurrence correlates strongly with poor patient satisfaction[265,266]. The number of patients requesting re-intervention for symptomatic recurrences are fewer than the total number of clinically evident recurrences, perhaps because of negative experiences with the primary surgery, but overall approximately 15–20% of varicose vein procedures are performed for recurrence[267].

Recurrence may be due to several factors, which are not mutually exclusive. Technically or tactically inadequate primary surgery, the growth of new incompetent vessels in a previously operated area (neovascularisation), significant untreated reflux in the below knee GSV, accessory trunks or perforators and disease progression have all been implicated in recurrence of SVI.

The increasing use of DUS from the 1990s, has led to gradual acceptance of the notion that recurrence of SVI after surgery is primarily caused by the process of neovascularization[58,262,263,268]. The pathogenesis of this phenomenon has not been fully elucidated; several factors are implicated in causality, which is essentially centred on the surgical trauma, including hypoxia, various growth factors such as vascular endothelial growth factor, vascularization of haematoma or scar tissue, free endothelial cells and elevated venous blood pressure[262,269-271].

These incompetent neovascular channels are typically seen arising in the groin from the region of the previously ligated and divided SFJ, or within the GSV strip-tract, and will ultimately communicate with either residual GSV or accessory pathways, feeding reflux into those vessels.

The results of SSV surgery are generally inferior to GSV surgery, both in terms of technical success and QoL outcomes. Patients undergoing SSV surgery can expect higher rates of residual or recurrent reflux, typically in up to 20-25% at between 6 weeks and 3 years[263,272], with clinical recurrence of up to 50% at 3 years.

### Quality of Life

Surgical treatment is superior to conservative management of varicose veins with compression therapy. In the REACTIV trial[221], as discussed previously, results of surgery with compression treatment were compared with results of compression treatment alone in 246 patients with varicose veins (C2 disease). Surgical treatment

involved conventional HTSA as detailed above. At 2 years, surgery afforded patients with statistically significant improvements in symptomatic relief, cosmetic results, and QoL over conservative management.

Due to its invasive nature and potential short-term complications (see below), however, there is an early postoperative impairment in QoL following surgery before any improvements are seen. An early cohort study of EVLA versus surgery from the Academic Vascular Surgical Unit in Hull showed significant deterioration in the physical domains of SF36 and also the AVVQ at one week compared to baseline values. These findings were also corroborated in the subsequent RCT, which will be discussed in further detail later[273,274].

Overall improvement in QoL from varicose vein surgery has been shown to be statistically significant by other well-designed studies[253,274] in addition to the REACTIV trial. Furthermore, the benefit is shown to be clinically meaningful and matches the benefits observed after other elective interventions such as laparoscopic cholecystectomy for cholelithiasis[275]. These QoL improvements have been shown to last for at least 10 years[265].

## Cost-effectiveness

The REACTIV trial cost-effectiveness data over a 2-year study period suggest that while surgery was more expensive than conservative treatment (£733 versus £345), surgical intervention falls well below the willingness-to-pay value of £20,000 per QALY[213], calculated at £4682 per QALY based on SF6D data[276]. Using EQ5D data (the adopted mechanism by NICE), this cost per QALY gained is even lower, at £3299. Additionally, the analyses were undertaken on an intention to treat (ITT) basis; it has already been highlighted earlier (see 1.4.1 Compression) that many patients allocated to the conservative therapy group switched to undergo surgical treatment, thus a cost-effectiveness analysis of surgery on a *per protocol* basis would be even more favourable.

### *Complications and Limitations*

There are several common complications and limitations of conventional surgery, including infection, delayed healing, haematoma and bruising, pain and neurological damage, vascular injury and recurrence. The overall complication rate for primary

GSV surgery is quoted at between 17% and 20%[277,278], while that for recurrent varicose veins is 40%[279]. Surgeons have attempted to address these complications and limitations through various technical modifications.

## Wound Infection and healing

Varicose vein surgery is classified as "clean" surgery, and therefore has an associated predicted wound infection rate of 1–5%[280-282]. There is, however, considerable variability in reported wound infection rates: up to 16 per cent has been reported in the literature[279,283,284]. This may be an underrepresentation, as currently the majority of operations are performed as a day case, with infections manifesting later in the community after discharge[285]. It has been shown that higher infection rates are reported when routine post-discharge wound surveillance is carried out[286].

The HARVEST (Hull Antibiotic pRophylaxis in varicose VEin Surgery Trialists) study from this unit[287] randomized patients undergoing conventional surgery to receive either a single intravenous dose of Co-Amoxiclav (antibiotic), or no antibiotic, prior to surgery. A modified ASEPSIS score was used as the primary outcome measure; this wound scoring method was developed for use in trials of antibiotic prophylaxis in the mid 1980's and first used in cardiac surgery to assess infection in sternotomy and vein harvest wounds[288]. The system awards weighted scores for 7 components (4 wound parameters and 3 related criteria) of wound infection:

- use of **A**dditional treatment (antibiotics, incision and drainage of abscess, or wound debridement)
- discharge of **S**erous exudates
- wound **E**rythema
- discharge of **P**urulent exudates
- **S**eparation of tissues
- **I**solation of bacteria
- prolongation of **S**tay in hospital for wound problems

This study revealed that patients who had prophylactic antibiotics prior to HTSA had lower ASEPSIS[288] wound scores on days 3, 5 and 7 (p=0.043, 0.032 and 0.003 respectively), and lower total ASEPSIS scores (median (iqr) 3 (0–9) versus 6 (0–15); p=0.013). They were less likely to consult their general practitioner (16.0% versus 24.3%, p=0.040) or to receive postoperative antibiotics (4.7% versus 13.5%, p=0.002) for wound-related problems.

Multivariate regression analysis from the HARVEST study showed that normal wound healing is less likely in current smokers, adjusted OR (95% CI) 0.5 (0.3-0.9) and with increasing BMI OR 0.92 (0.87-0.97) per mg kg$^{-2}$ increase[287], a pattern also identified in other studies of surgical wound healing[289].

## Neurological Complications

Conventional varicose vein surgery has been reported as the single commonest cause of medicolegal action against general and vascular surgeons[290,291], predominantly due to injuries to the saphenous and sural nerves, which lie in close proximity to the GSV and SSV respectively. The below-knee saphenous nerve and GSV are intimately related, thus below-knee GSV stripping significantly increases the rate of nerve injury[292,293]. In a RCT of full length stripping versus stripping to the knee, the reported nerve injury rates were 39% and 7% respectively (p<0.001)[258]. However some authors have asserted that compared to full length stripping, in terms of residual or recurrent SVI, the long-term results of GSV stripping to the knee are worse and that the length of GSV stripping should be dictated by the length of refluxing vein rather than concerns over injury to the saphenous nerve[294]; this view remains controversial. Furthermore, whilst the rate of neurological injury may be lower, it has long been established that SFJ ligation without GSV stripping results in unsatisfactory recurrence rates[58,255]; in the study of ligation alone versus ligation and stripping by Dwerryhouse et al[255], reoperation rates were significantly higher in the former group (20% versus 6%, p=0.02) over five-year follow up.

There are no definitive data on the rates of sural nerve injury following surgery for SPJ and SSV reflux. However, indirect information gathered from medicolegal claim data show that 7.5% of claims following venous surgery were related to sural nerve injury[295]. Common peroneal nerve injury is reported at between 2% and 4.7%[296]. It is unclear as to what proportion of these injuries can be ascribed to either the popliteal fossa dissection or the axial stripping[293].

Adjunctive procedures, such as phlebectomy and perforator treatments are also associated with nerve injury, but there are no reliable data to quantify their incidence, which is clearly compounded by the extent to which such procedures are required or routinely performed.

## Venous Thromboembolism

The incidence of venous thromboembolism (VTE) has previously been reported to be very low following conventional surgery[277]; a Cochrane review reported rates of PE and DVT at 0.48-0.62% and 0.96% respectively[297]. Since the routine use of DUS more recently, however, the incidence of post-operative DVT could be as high as 5%, although the majority of these are asymptomatic and confined to the calf veins with no subsequent propagation or clinical evidence of PE[298]; around 50% of observed DVTs resolve without evidence of DVI at 1 year.

## Iatrogenic vascular injury

A 2007 systematic review of the literature reported an overall incidence of iatrogenic arterial and venous injury of 0.002%-0.3% following conventional venous surgery[299]. Clearly there will be a certain degree of negative publication bias, but overall the incidence would probably still be well below 1%, although the consequences of such injury do typically have high morbidity and mortality rates.

## *Technical Modifications*

### Reducing Groin Neovascularisation

Various technical modifications have attempted to reduce groin neovascularization. Whilst some successes have been reported, the overall outcomes have largely been disappointing and none have made it into routine widespread practice.

A number of studies have investigated modifications of standard SFJ ligation. A RCT of standard versus flush SFJ ligation[300] found no differences in neovascularization, clinical recurrence or AVVQ scores at up to 2 years; unfortunately the study was not sufficiently powered due to a significant participant drop-out rate. A cohort study compared 70 limbs that underwent conventional surgery (control group) with 65 limbs undergoing complete resection of the GSV stump with inversion suturing of the CFV venotomy (intervention group). Again, at two years, there were no differences in either overall (43% versus 49%, p=0.592) or clinically significant neovascularization (9% versus 20%, p=0.127) between the control and intervention groups respectively[301].

Several studies have investigated the use of barrier techniques as a method of decreasing recurrence secondary to neovascularisation. These techniques have included closing of the cribriform fascia[302], suturing a reflected flap of fascia[303,304] or

using a prosthetic patch such as PTFE[305,306], Dacron™[307] or silicone[261], in an effort to physically separate the CFV and SFJ stump from the superficial venous compartments. Some of these modified techniques, particularly those using prosthetic material, have resulted in either short- or long-term complications[308]. A reduction of neovascularization of more than 50% has been shown with the other techniques, but again the overall recurrence rates of the modified groups do not appear to be significantly better than those reported by large-scale studies of conventional technique from other centres. The disappointing results are also evident in autologous tissue techniques; a study of patients undergoing redo surgery for recurrence with a barrier created by suturing a reflected flap of pectineus fascia demonstrated no significant reduction in re-recurrence rates[304].

Given that haematoma is thought to promote neovascularization, it may be argued that it is not specifically the technical modifications themselves but the more fastidious surgical approach required in these techniques that inherently results in lower rates of haematoma formation[300], which have been reported in up to 33% of postoperative cases[309], and hence less neovascularization.

### Reducing strip-tract haematoma

In addition to haematoma formation and subsequent neovascularization in the groin, the same phenomenon has been widely observed within the GSV strip-tract. It has also been suggested that strip-tract haematoma is the single-most important factor in determining postoperative pain, recovery and QoL in patients undergoing surgery[310], and can last for up to six weeks[278].

### Cryostripping of the GSV

To decrease hemorrhage along the GSV strip-tract and avoid any incision placed at the level of the knee, the technique of cryostripping has been suggested by some investigators[311], as an alternative to PIN stripping. The technique is relatively new and has not been fully evaluated, nor is it commonly practiced in the UK. In this technique, a cryosurgical system (Erbokryo CA, ERBE Elektromedizin GmbH, Tübingen, Germany), powered by liquid nitrogen, is used. After high ligation is completed in the standard fashion, the cryoprobe is inserted into the GSV and passed down to the level of the knee. Once the probe tip reaches the desired segment of the GSV, freezing with liquid nitrogen is initiated. After the freezing cycle is maintained

for a few seconds, the GSV is invaginated with an upward tug and stripped to the groin.

A RCT compared a total of 160 patients randomised to either conventional surgery or surgery with cryostripping[311]. While there was a significant reduction in the mean area of thigh bruising (161cm$^2$ versus 123cm$^2$, p=0.010) with cryostripping, it is doubtful whether this has any clinical significance, as there were no statistical differences between the groups in terms of pain scores, QoL (SF36), incidence of haematoma or paraesthesia. Long-term results on recurrence are still awaited.

### Anaesthetic Technique

Standard conventional surgery for SVI in the UK NHS is predominantly performed under GA, with a smaller number of patients undergoing spinal anaesthesia. Practices in continental Europe have more experience with surgery using LA, often in combination with a femoral nerve block.

In a non-randomised clinical trial, patients scheduled to undergo varicose vein surgery were asked to choose between LA or GA[312]. Overall, there were no differences between the groups in terms of postoperative pain scores. Additionally, the study had a number of methodological issues. The surgical technique was not the gold-standard HTSA, but segmental avulsion of the GSV, and hence less invasive than conventional surgery. Mean baseline AVVQ scores were significantly higher in the GA group (10 versus 15.6, p=0.007), which was also significantly younger (48 versus 36 years, p=0.0164) and had higher BMIs (24 versus 30, p=0.0168) than the LA group. *Post-hoc* calculations also revealed the study to be underpowered. Furthermore, neuropraxia was reported in 33% of participants, which is high in comparison to other studies[258].

A number of other studies have looked at using tumescent local anaesthesia (see description of technique later, p.81) for HTSA. However, the technique is typically combined with sedation and/ or femoral nerve blockade. Thus, this is not the truly walk-in, walk-out procedure as that of endovenous approaches.

### Surgery with GSV preservation

Based on the "ascending" theory of SVI, eradication of varicose GSV tributaries would, in principle, restore competent flow to the main trunk, which can then be preserved and used as bypass conduit at a later time, if needed; GSV is the most

commonly-used conduit for arterial bypass surgery. There are chiefly two techniques associated with this concept.

### 1) CHIVA

This technique, developed by Franceschi in the late 1980s and 1990s is named "ambulatory conservative hemodynamic correction of venous insufficiency" (In French: *cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatoire* [CHIVA])[313]. The aim of CHIVA is preservation of the GSV and normal venous drainage of the superficial tissues of the lower limb, based on careful haemodynamic assessment with DUS. The technical principles underlying the CHIVA method are segmentation of the venous pressure column, elimination of perforators with deep to superficial reflux ("shunts'), preservation of perforators with antegrade flow and abolition of undrained superficial varicose veins. Reverse flow within the GSV or other trunks is maintained, provided it is subsequently drained into the deep venous system[314,315]. The concept is generally implemented by open surgery under LA, but sclerotherapy, EVLA and RFA have also been used.

There are two notable RCTs in the English language that compare CHIVA (implemented by open surgery) with conventional surgery (HTSA). Carandina *et al*[316] reported that over a mean follow-up of 10 years, CHIVA resulted in significantly lower recurrence of varicose veins (18% versus 34%, P<0.04); there were no differences at three years. However, participant attrition during the follow-up period was quite high and there was no reported power calculation. Furthermore, the inclusion criteria were very selective, which may have favoured patients in the CHIVA group. The second study[317] gave similar results in terms of freedom from recurrence. Data on patient satisfaction and QoL were not reported in either of these studies, nor has there been any health economics analysis of cost-effectiveness.

The technique is not commonly used outside of France, Italy and Spain and indeed seems to have been usurped by the development of endovenous techniques. Whilst a few enthusiasts of the technique have reported respectable outcomes, these have not been replicated by other groups[318].

## 2) ASVAL (Ambulatory Selective Vein Ablation under Local anaesthesia)

The ASVAL technique (ambulatory selective vein ablation under local anaesthesia), involves ambulatory phlebectomy of all varicosities, with truncal preservation, irrespective of its competence[319]. A retrospective case series of 811 legs in 599 patients with varicose veins in the context of SVI has shown some improvements in haemodynamics, signs and symptoms. After four years, 66.3% of previously refluxing veins (greater than 0.5 seconds) had reverted to competence (less than 0.5 seconds reflux). However, the patient cohort was not representative of standard NHS referrals; the overwhelming majority of patients (85.8%) had C2 disease, there were no patients with CVI, and one third of patients were asymptomatic. Notwithstanding such a high proportion of early and asymptomatic disease, the authors reported 11.5% recurrence by 4 years, with the same number of patients undergoing a second procedure.

DUS evidence from studies of GSV stripping also gives a counter-argument to treating SVI according to the "ascending" theory; as described earlier, in patients where the GSV is stripped to the knee, the rate of post-operative below-knee residual GSV reflux is significantly lower than in patients who undergo SFJ ligation without stripping[58,255].

## 1.4.4 Sclerotherapy

## Liquid Sclerotherapy

The technique of liquid sclerotherapy was first described by Chassaignac in 1855 and relies on the basic principle of using an injected chemical to induce inflammation in the endothelial and subendothelial layers of the vein wall, resulting in its subsequent fibrosis, with luminal obliteration. Weak sclerosants may cause no endothelial injury, whereas damage to normal vessels will occur if the sclerosant volume or concentration is too high. Historically, various sclerosant chemicals have been used to invoke this intraluminal fibrosis, but early sclerosant formulations were beleaguered by significant side effects and unacceptably high recurrence rates, causing the technique to fall out of favour with vascular surgeons.

Modern sclerosants can broadly be categorized into three types[320], according to their mechanism of action:-

- Detergent sclerosants – Cause disruption of vein cellular membrane by altering surface tension, resulting in cell maceration
    - Sodium tetradecylsulphate (STD)
    - Polidocanol
    - Sodium morrhuate
    - Ethanolamine oleate

- Osmotic sclerosants – Cause osmotic shift of water, resulting in cell wall damage by cell dehydration and membrane denaturation
    - Hypertonic sodium chloride solution
    - Sodium chloride and dextrose solution

- Chemical irritant sclerosants - direct caustic destruction of vein endothelium
    - Chromated glycerine
    - Polyiodinated iodine

The two main chemicals currently used for sclerotherapy are the detergent sclerosants polidocanol and STD. These are available in various concentrations, depending on the size of the vessel to be treated.

*Technical Success and Recurrence*

Following the work and publications of Fegan in the 1950s and 1960s, liquid sclerotherapy was re-popularized. Fegan's seminal report on results from 13,352 people treated with his technique quoted a recurrence rate of less than 15% at six years (in a sample of 760 people)[321], and provides a detailed description of compression methods to achieve successful sclerotherapy, and improve outcomes. However, these suggestions are not supported by the evidence from a Cochrane review of injection sclerotherapy[322], where neither the type nor duration of compression used following sclerotherapy had any statistically significant effect on the obliteration of varicose veins or long-term recurrence rates. A more recent RCT also produced the same findings[323]. Fegan used 3% STD (0.5 ml per injection) for sclerotherapy and this is generally considered as the gold standard sclerosant, although the Cochrane review also fails to show any differences between STD or its alternative sclerosants. This may be due to considerable heterogeneity in technique.

There are actually very few RCTs that have compared what is now considered as conventional surgery (HTSA) with injection sclerotherapy. Many other studies have looked at various hybrid procedures, such as high-ligation with sclerotherapy to the axial vein and varicosities, thus making firm conclusions on efficacy of the technique difficult. Additional issues arise from the fact that these early studies were conducted before any consensus on reporting or outcome standards in SVI were formulated.

In the studies included in the Cochrane review that compared sclerotherapy to junctional ligation without stripping, one RCT found surgery to be subjectively and objectively better than sclerotherapy at 3-year follow-up ($p < 0.05$)[297]. As stated earlier, it is widely accepted that stripping of the GSV significantly reduces recurrence rates, thus these results are not at all favourable for liquid sclerotherapy.

The more recent REACTIV trial of liquid sclerotherapy versus surgery identified that following surgical treatment, 76% of patients had no visible varicosities at 1-year follow-up, compared with 39% following sclerotherapy ($p < 0.05$).

In a comparison of liquid sclerotherapy (3% STD) versus conservative therapy, the REACTIV trial[221] reported significantly more patients with an improvement in the anatomical extent of their varicose veins following sclerotherapy compared with conservative therapy (84.6% versus 28.6%, $p < 0.05$) at 1-year follow-up. The sclerotherapy arm also demonstrated a significantly greater reduction in aching

symptoms ($p<0.05$).  At 2-year follow-up, however, 76.9% had developed new varicosities, with no significant difference between the treatment groups.


### Complications

Fegan described a number of techniques to reduce complications, such as continuous compression following injection in order to avoid superficial thrombophlebitis.  As with technical success rates, however, a systematic review failed to show any significant benefit of these techniques[322].


In the REACTIV trial, early complications following sclerotherapy included phlebitis (15.4%), skin staining (7.7%) and skin blistering or ulceration (7.1%). An additional 38% of patients reported skin staining upon direct questioning; the only adverse event following compression therapy was a 6.6% incidence of phlebitis.  Within the same study, similar complication rates were also reported in the sclerotherapy versus surgery cohort[221], although reports of phlebitis and intraluminal haematoma have been even higher in other studies[297].


### QoL

In the REACTIV trial study of compression versus liquid sclerotherapy, QoL assessments, including SF6D and EQ5D, were no different between the groups at 1- or 2-year follow-up.


At one-year follow-up in the surgery versus liquid sclerotherapy study within the REACTIV trial, the surgical group demonstrated significantly better EQ5D scores. Although this difference was also evident at two years, it did not reach statistical significance.


These unsatisfactory results in the context of RCT evidence caused many practitioners to turn away from liquid sclerotherapy for the treatment of junctional and axial disease, either to the alternative of foam sclerotherapy, or the newer endovenous thermal ablation procedures, which were emerging at the same time as this negative evidence.

## Ultrasound-guided Foam Sclerotherapy

The development of ultrasound-guided foam sclerotherapy (UGFS) sparked a renewed interest in sclerotherapy. In this technique, the GSV (or other axial vein) is cannulated under ultrasound guidance and sclerosant foam, produced by vigorously mixing the liquid sclerosant preparation with air, is injected. The foam physically displaces blood within the vein, which reportedly enhances the efficacy of the sclerosing agent by reducing the volume of sclerosant required for treatment and increasing the effective surface area of the sclerosant in contact with the vein wall. Ultrasound visualization of the foam allows a more targeted approach and is prevention of significant spread of the foam into the deep veins.  A major proposed advantage of foam sclerotherapy over conventional sclerotherapy is that larger veins appear to be successfully treated with the foam technique compared with liquid sclerotherapy[324].

Several techniques have been proposed to produce sclerosant foam, but the Tessari technique[324] appears to give the most favourable results and is in most widespread use.

### Technical Success and Recurrence

The authors affiliated with the Tessari technique reported a case series of 196 patients treated with that method of UGFS.  Both SFJ/GSV and SPJ/SSV disease were included, encompassing both "minor-" and "medium-large-" varicose veins; no further description of disease severity, VCSS or CEAP was given.  The study reports a 93% success rate based on "clinical and instrumental follow-up" ranging from 20 to 180 days.

Two RCTs have compared foam sclerotherapy with an equivalent standard liquid formulation. Hamel-Desnos[323] randomised 88 participants to either UGFS with 3% polidocanol, or the same strength sclerosant as liquid injection.  At 3-week follow-up, the UGFS group had a significantly higher rate of reflux elimination compared to the liquid group (84% versus 40%, $p<0.01$).   However, recanalisation rates at six months were no different between the two techniques. The VEDICO (VEnous DIsease COntrol) trial[325] compared a number of different treatments for varicose veins (low- and high-dose liquid sclerotherapy, UGFS, and two non-standard surgical treatments). The failure rate and incidence of recurrent varicose veins at 5 and 10 years was no different between foam and liquid formulations[325].  However, the 10-year recurrence rate was 51.2%.

Many case series by enthusiasts of the technique have described good early results with UGFS, but only a few have included follow-up beyond three years, with successful occlusion rates reported at around 80% up to 5 years[326-328]. A NICE-commissioned systematic review of 69 studies of UGFS[329] reported an 87% complete abolition of reflux in treated veins, while recurrence or development of new veins occurred in 8.1%. However, the follow-up periods in the included studies were relatively short. Meta-analysis for complete occlusion within this review suggested that UGFS is less effective than surgery (RR 0.86 [95% CI 0.67-1.10]) but more effective than liquid sclerotherapy (RR 1.39 [95% CI 0.91-2.11]), although there was substantial heterogeneity between studies in terms of sclerosant used, concentration, foam production method and anatomical disease. A later meta-analysis reported similar UGFS success rates of 82.1% at 3 months and 73.5% at 5 years[330].

### QoL

QoL had been poorly studied in UGFS at the commencement of this MD.

### Complications

Proponents of UGFS cite the procedure as being a quick, simple, office-based procedure, which is both cheap to perform and repeatable. The Tessari technique authors reported a 3.6% rate of phlebitis, and an overall complication rate of 7.1%, including DVT, malaise, visual disturbance and skin necrosis.

Critics of UGFS have raised a number of concerns, not just over the relatively high technical failure and clinical recurrence rates as discussed above, but also the potential serious adverse events. Neurological sequelae of the technique are a particular concern; rates of visual disturbance and headache have been reported at 1.4% and 4.2% respectively[329], while a further systematic review of 10,819 patients found that there was an overall 0.9% rate of neurological complications, including migraines (0.27%), stroke (0.1%) and transient ischaemic attack (0.1%)[331]. Eleven of the 21 patients confirmed as having CVA in this series were shown to have right-to-left cardiac shunt, usually a patent foramen ovale (PFO). Other serious adverse events such as PE and DVT are reported at less than 1%, while the median rates of thrombophlebitis and skin staining/pigmentation appear similar to earlier studies of liquid sclerotherapy at 4.7% and 17.8% respectively[329].

## 1.4.5 Endovenous Thermal Ablation

The underlying principle of this treatment modality is to deliver thermal energy of sufficient magnitude to the wall of an incompetent vein to cause irreversible luminal occlusion, followed by fibrosis and ultimately resorption of the vein[332]. The first results of a similar concept technique, using electrocoagulation, were published in 1966, but the outcomes were marred by high complication rates including skin burns, injury of the saphenous and peroneal nerves, phlebitis, and wound infection[333].

The two endovenous thermal ablative treatments that have achieved mainstream use over the last decade are radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). Both techniques involve the percutaneous access and seldinger insertion of a catheter into the superficial truncal vein to be treated, under ultrasound guidance, with the tip positioned just distal to the superficial-deep junction (i.e. SFJ/SPJ).

Both techniques rely on the use of tumescent local anaesthesia, which fulfills a number of functions:-

1) Anaesthesia
2) Hydrodissection of surrounding soft tissue and nerves away from the vein
3) Acts as a heatsink, protecting surrounding tissues and skin from thermal damage
4) Compresses the axial vein and inflow tributaries, thereby eliminating luminal blood, placing the intima in closer proximity to the heatsource to give a more uniform treatment.

Under ultrasound guidance, this fluid is infiltrated around the vein(s) to be treated typically using a peristaltic pump and spinal needle, the length and steerability of which reduce the number of percutaneous punctures required. A more detailed and specific review of tumescent anaesthesia is covered later (see Tumescent anaesthesia, p.101)

Thermal energy, from either a radiofrequency or laser generator, is then applied into the target vein. As the laser fibre or RFA catheter is withdrawn down the length of the vein, thermal damage is inflicted upon the venous endothelium and into the wall, resulting in contraction and ultimately destruction of the vessel; the specific

mechanism of energy delivery and subsequent effects on the vein wall differ between the techniques and are further discussed below.

The fact that these procedures can be performed in an outpatient setting, without the need for general anesthesia, allows for a walk-in/walk-out procedure with minimal postoperative recovery time.

## Radiofrequency Ablation

Radiofrequency energy has been applied in various therapeutic settings within medicine, such as for ablation of abnormal arrhythmogenic cardiac conduction pathways[334], and more recently for minimally-invasive treatment of some solid-organ tumours. In 1999 the method of endovenous RFA using the VNUS® Closure™ catheter for treatment of SVI was approved by the USA Food and Drug Administration (FDA). Refinement of this bipolar catheter produced the ClosurePlus™ catheter in 2003.

The Closure™ and ClosurePlus™ systems heated the vein to 85°C, by using the vein wall as a resistive element between bipolar electrodes. The technology had some significant disadvantages compared with EVLA. These were slow pullback speed (the recommended 2-3cm min⁻¹ pullback rate equated a 20-25 minute withdrawal time for a typical SFJ to knee level treatment length) and the need to ensure complete exsanguination of the treated vein to obtain perfect apposition of the electrodes and the endothelium. Failure to achieve this would require the operator to repeatedly remove the catheter in order to clear coagulated blood from the bipolar electrodes, thus further increasing the treatment time. Coupled with the modest (if any) improvement in technical success and clinical outcomes over conventional surgery (see below), these limitations meant the procedure did not secure widespread adoption by vascular surgeons. Specialist advice on the technique of RFA was sought by NICE from the Vascular Surgical Society of Great Britain and Ireland in 2003[335]. The consensus view at that time regarded RFA for varicose veins as a "novel procedure" and " more complicated to perform than standard alternatives" despite similar risks and benefits. Particular concern surrounded the risk of recurrence, with an overall feeling that the technique was unlikely to disseminate widely in the NHS[335]. However, it did provide a tantalizing glimpse of how the endovenous treatment of SVI may evolve.

Redesign of the ClosurePlus™ RFA device resulted in the ClosureFast™ (VNUS Medical Technologies, San Jose, California) segmental ablation system, approved by the FDA in 2006 and making an entry into worldwide clinical use between 2006 and 2008 (the system is now rebranded as the VENEFIT™ procedure, after acquisition by Covidien for approximately $440m US in 2009). This device achieves endovenous ablation using a catheter with a 7cm long heater-coil at its tip, which is used to generate temperatures of 120°C, maintained for a 20 second cycle at each 7cm treatment segment; energy delivery is automatically regulated using a feedback loop between a temperature sensor in the catheter tip and the RFA generator unit. The catheter is withdrawn in 6.5cm stages, to allow a 5mm overlap between each treated venous segment. This system is significantly quicker to perform than its predecessor, with the manufacturer also claiming superior closure rates and lower post-procedural pain.

A further device, RFiTT™ (RadioFrequency induced Thermal Therapy) (Celon, Olympus), arrived into clinical use in the NHS at around the time of commencing this MD project; it works on a similar principle to the original VNUS Closure device, i.e. resistive ablation via bipolar energy delivery, with an optimal pullback speed of 1–1.4 cm/ second[336]. Evidence for its efficacy was sparse at the onset of this programme of work[336].

### Technical Success and Recurrence

From early RCTs of Closure™ / ClosurePlus™ versus conventional surgery, immediate treatment success, defined as complete GSV occlusion (or absence in the case of surgery), ranged from 81.3 to 100% in patients receiving RFA and 87.5 to 100% in patients receiving surgical intervention[337-340]. There were no RCTs of ClosureFAST versus conventional surgery at the commencement of this MD programme.

Lurie *et al*[338] reported 100% of limbs receiving surgery to be reflux-free at 72 hours and one week follow-up, versus 88.4% of limbs receiving RFA in the EVOLVeS trial; by 4-month follow-up reflux was resolved in one of the RFA limbs, leaving a total of 90.7% of RFA-treated limbs free from reflux. At two-year follow-up, 41% of GSVs treated by RFA were undetectable on DUS, while a further 51% demonstrated progressive shrinkage; however, 16.3% of RFA limbs had patent GSVs compared with 8.3% of GSVs in surgery limbs[309]. Neovascularization occurred in one (2.3%) and

four (11.1%) limbs treated with RFA and surgery respectively[309]. This difference was not statistically significant, nor was the cumulative rate of recurrent varicose veins at 1- and 2-year follow-up between the groups (RFA=14.3%, Surgery=20.9%).

Another RCT also found the clinical recurrence rate to be not significantly different between RFA and surgery (ligation and stripping only) at 3-year follow-up[341]. The same RCT found rates of venous occlusion and recanalization/neovascularization to not differ significantly between the groups. Significantly more patent superficial inferior epigastric veins were found in the RFA group (100%) than in the surgery group (38%) (p< 0.0001), although the clinical significance of this is not known.

A 2005 report from a prospective international registry of Closure™ / ClosurePlus™ for SVI reported five-year clinical and anatomical outcomes in 1006 patients (1222 legs)[342]; technical success at five years was reported at 87.2%. This was followed by a 2006 report of a nonrandomized comparative study, which found 10.9% of surgically treated limbs displayed reflux and evidence of neovascularization compared with no limbs from the RFA group (p = 0.028) at one-year follow-up[339].

A 2008 systematic review and meta-analysis reported a four-year clinical recurrence rate of 22%[343]. Recurrent varicosities were seen in 27% of patients at five years and anatomical failure of Closure™ / ClosurePlus™ was an independent risk factor for varicosity recurrence.

In a 2009 meta-analysis, the technical success (occlusion rate) following Closure™ / ClosurePlus™ was reported to be 89% and 80% at three and 60 months, respectively[330]. Whilst comparing favourably to surgery and UGFS, these rates were lower than for EVLA (see Endovenous Laser Ablation, p.86).

A 2008 report of outcomes in an early series of 252 GSVs (194 patients) receiving ClosureFast™[344] reported an occlusion rate of 99.6% at six months, although there was a significant loss to follow-up, with only 74 of the original 252 limbs being assessed at this time point. The same group published further results from a cohort of 225 patients (295 GSVs) at one-[345] and three-year[346] follow-up. It is not clear, but seems likely, that these reports also included the earlier-reported 252 GSVs (all studies reportedly commenced treatment in April 2006). At one, two and three-year follow-up, the complete occlusion rates were 96.3%, 94.5%, and 92.6% respectively; freedom from axial reflux was observed in 99.0%, 97.2%, and 95.7% of GSVs at the same respective

time-points. Of the 256 GSVs assessed at three years, 4.3% had undergone subsequent treatments – one repeat ambulatory phlebectomy & 10 sclerotherapy.

Regarding the RFiTT device, no RCTs versus conventional surgery were published at the commencement of this MD.

### Clinical Outcomes and Complications

In terms of clinical severity, one RCT reported a significant difference in VCSS, favouring RFA over surgery (ligation with stripping) at 72 hours and one-week follow-up (p<0.05)[338]; however, this significance disappeared at all subsequent time points up to two years[309]. Rautio *et al*[337] found no statistical difference in VCSS improvement between the groups at 50-day follow-up.

Significant improvements in various symptoms of SVI such as pain, fatigue and swelling have been reported in both the short-term[3,6] and up to five years[7], even in cases where recurrent axial reflux was identified[342].

In the prospective case series of ClosureFast™ by Proebstle *et al*[344], 70.1% of treated limbs reported no post-procedural pain; this is contrasted with an earlier study of EVLA by the same research group[347], that reported in excess of 70% of patients experiencing pain, although the precise pain levels were not reported in that paper, so it is clearly difficult to derive any meaningful conclusion in this respect.

Paresthesia and skin pigmentation have been reported in 3.4% and 3.1% of cases undergoing ClosureFast™[345]

### QoL

Notwithstanding the relatively high technical failure/recurrence rates with the early RFA devices, the technique was reported to have other benefits including superior short-term QoL, when compared with conventional surgery[309,337,340], although these differences had generally converged by one month.

Only a few RCTs measured QoL response to treatment[309,337,338,341], and their methods were heterogeneous. Rautio *et al*[337] used the SF36 to assess treatment effectiveness and found a trend towards improved physical functioning scores (Median [IQR]) 30 (21-48) for RFA, 50 (35-65) for surgery, (p=0.07) and bodily pain scores 23 (5-24) for

RFA, 38 (20-45) for surgery (p=0.05) at 1-week follow- up.  However, this difference was not maintained to four weeks. Similarly, the EVOLVeS trial, using CIVIQ-2, found improvement in global pain and physical domains at 72 hours and one week following RFA (p=0.003)[338].  Longer-term follow-up from this study[309] found pain as a QoL domain was consistently reduced in the RFA group throughout follow-up (up to 2 years), in both absolute score and difference from baseline (p<0.05). In this population, the significant difference in pain scores in the CIVIQ-2 instrument, favouring RFA over surgery, was present at 72 hours and one week, disappeared after 3 weeks, remained absent at four months, but reappeared again at 1 year and remained at 2 years.  This clinical relevance of this seems difficult to explain.

A RCT of ClosurePlus[™] versus surgery reported in 2010 showed statistically significant improvements in AVVQ scores over baseline for both groups at five weeks, and there was a trend to lower (better) scores in the RFA group compared to surgery but this was not statistically significant[348].

In the RFiTT study[336], the authors are not explicit about whether there were any statistically significant improvements in mean AVVQ scores between baseline (3.99) and 6-month follow-up (3.55), however this change is unlikely to be of clinical significance.   Furthermore, the baseline scores were much lower than would be expected from most patients with symptomatic SVI.


## Endovenous Laser Ablation

Simultaneous with the development of RFA, endoluminal lasers were also demonstrated to effectively abolish reflux through thermal damage to the venous endothelium; the use of endoluminal laser energy for the treatment of SVI was first reported in 1999[349], with the first case series from the same group published two years later[350,351].

From a technical perspective, the procedure is broadly similar to RFA; in lieu of a radiofrequency catheter, EVLA utilises the delivery of laser energy into the vein via an optical fibre. The term "laser" originates from the acronym *Light Amplification by the Stimulated Emission of Radiation*.  It is a beam of coherent (in-phase), collimated (parallel / low divergence) photons; this allows a very intense and accurate delivery of monochromic energy, i.e. the same "colour" or wavelength.  While the word "light" is

used in the acronym, any wavelength of energy along the electromagnetic spectrum can be used, such as visible light, infrared, ultraviolet, microwave or x-ray. The effects of laser energy on biological tissue are determined by the specific laser wavelength and the chromophore in the target tissue with which it interacts. EVLA uses wavelengths in the "near-infrared" spectrum. *In vivo*, this electromagnetic energy is absorbed and converted into thermal energy by specific tissue chromophores Haemoglobin is the chromophore for shorter laser wavelengths (810, 940 and 980nm), whereas intra- and extracellular water[352] in the vein wall are the chromophores for the newer, longer wavelength (1319, 1320 and 1470nm) lasers. EVLA is subject to stringent laser safety practices, and hence cannot be performed in a typical "office" setting, unlike RFA.

In addition to altering the wavelength of laser energy, EVLA may be modified in a number of ways (see Optimising the EVLA technique, p.101):-

- power (Watts): Typically 12-14W for the short and 10W for the long wavelength lasers
- Pulsed or continuous mode
- Fibre type: Initial EVLA fibres were "bare" tipped. More recently the novel refinement of the fibre tips has evolved in an attempt to improve efficacy (e.g. radial-firing, jacketed- and tulip-tips)
- Magnitude of energy delivery (LEED/endovenous fluence equivalent, see p.106)

There are several theories surrounding the precise mechanism by which laser energy results in venous occlusion, including the optical–thermal response of the vein wall to laser light, the thermal response of the vein wall to steam bubbles, and direct contact between the hot laser fibre tip and the vein wall[353-355]. Much of the histopathological evidence is based on the early, lower wavelength lasers (810, 940 and 980nm). Proebstle *et al*[356] identified an instrumental role of intravascular blood in thermal damage to the vein wall during lower wavelength EVLA in *ex vivo* experimentation. While laser-induced vessel wall injury in saline-filled veins was confined to the site of direct laser impact, blood-filled veins exhibited more widespread thermal damage, including the vein wall opposite to the laser impact. Laser energy from these lower wavelengths generated steam bubbles in blood, while no bubbles could be produced in normal saline or plasma.

Other theories cite the combined effects of vein spasm, compression by perivenous tumescent anaesthesia and ablation in the Trendelenberg position results in an 'empty' vein and direct thermal damage to the vein wall. This is supported by several histological studies that show intimal damage combined with discrete full thickness perforations and relatively 'normal' intervening vein wall[357].

Early EVLA results predominantly came from single-centre case series, compared to the multicenter reports for early RFA, which were therefore considered more reliable in terms of standardization of study protocol and data collection. Recently, however, a handful of RCTs and meta-analyses have confirmed the short-term technical efficacy and other benefits of EVLA in comparison with surgery[358-364].

### Technical Success and Recurrence

"Technical" or "anatomical" success following EVLA has been considered in a number of ways, with definitions including abolition of reflux in the treated vein, overall ablation or occlusion rates and freedom from recanalization, where flow may be either normal, or recurrent reflux. Figures for "success" have also conversely been reported as "failure rates". These definitions can be applied to both the SFJ and GSV (or other axial vein) together and/or independently. Clinical success is typically judged by freedom from recurrence of clinically apparent varicosities in a previously treated venous distribution.

In an early cohort study of EVLA (810nm 14W continuous mode) versus Surgery from the Academic Vascular Surgery Unit in Hull, GSV ablation rates following EVLA were 99% and 96% at 1- and 12-week follow-up, respectively. SFJ occlusion rates of 97% and 96% respectively were seen at the same time-points[273]. Limited early evidence suggested that EVLA provides a durable closure; in a large single centre report of EVLA in 1250 patients, the recanalization rate was 3% at 3 years[365].

A meta-analysis of conventional surgery, UGFS, RFA and EVLA published by van den Boss et al[330] in 2009 suggested that EVLA provides successful eradication of reflux in 93.3% (95% CI, 91.0-95.0) of patients, independent of time of follow-up; there was no observed significant negative trend to success over time, unlike that seen with conventional surgery[330]. However, this meta-analysis only includes studies published prior to February 2007, at which point there were no published RCT data for EVLA in comparison with conventional surgery. The findings must therefore be

interpreted with caution, owing to the high degree of study heterogeneity, including both non-randomised and non-comparative series of EVLA, performed by enthusiasts of the technique. Furthermore, success was only measured in terms of technical DUS outcomes, without any analysis of clinical recurrence rates.

Subsequent to this early meta-analysis, a handful of RCTs have been performed that compare EVLA with conventional surgery. There is substantial heterogeneity in methodology, outcome measures and study limitations across these trials, thus requiring each study to be considered in some detail before meaningful comparisons can be made.

A RCT by Rasmussen *et al* from Denmark[358] was the first true randomized trial to compare patients with SFJ/GSV insufficiency undergoing either conventional surgery (59 patients, 68 legs) or 980nm, 12W pulsed mode EVLA (62 patients, 69 legs). Abolition of reflux in the treated GSV segment was achieved in 92.8% and 97% at 12-days and in 94% and 98% at 6-month following EVLA and surgery respectively. Two GSVs in the EVLA group experienced recanalization at 3 months and another at 6 months; these patients, along with two surgical patients in whom the GSV snapped during stripping, subsequently underwent UGFS and were excluded from the study[253]. This study has a number of methodological deficiencies. Loss to follow-up was significant; 22% in the EVLA group and 26% in the surgery group. This attrition was not accounted for in the original power calculation, which suggested 60 patients were required per group. No statistical comparison of rates of abolition of reflux was performed; the potential for selection bias was significant, given that randomisation was undertaken in blocks of 10 sealed envelopes; only 121 of 1135 screened patients were apparently eligible; and no CONSORT diagram was presented.

Two-year follow up of this study was published in early 2010[253]. Clinical recurrence (defined as a varicose vein that had not been previously observed or marked by the patient on question 1 of the AVVQ form) was found in 25 (37%) and 18 legs (26%) in the surgery and EVLA groups, respectively (difference reported as not statistically significant).

Darwood *et al*[359] performed a 3-arm study of EVLA 12W pulsed mode (EVLA 1) versus EVLA 14W continuous mode (EVLA 2) versus conventional surgery. Considering the primary outcome measure of abolition of DUS-detected reflux at 3

months, both EVLA modalities and surgery had equivalent technical success at both the SFJ and GSV. While the power calculation required 92 patients per group (276 overall), the study only achieved randomization of 49, 42 and 45 patients to each arm respectively. In addition to poor recruitment, there was significant loss to follow-up. At 3 months GSV reflux was abolished in 41 of 42 legs treated with EVLA 1, in 26 of 29 treated with EVLA 2 and in 28 of 32 treated surgically (p = 0.227).

Kalteis et al[361] randomised patients to either conventional surgery or SFJ ligation and EVLA of the GSV. The EVLA was 810nm, pulsed mode, with graduated reduction in power from 10-12W in the thigh down to 4-6W at the lower leg, and an overall target LEED in the region of 20-30Jcm$^{-1}$. All procedures were performed under GA, and no tumescent anaesthesia was used. Successful eradication of GSV reflux at 7 days was 95.7% and 97.9% for EVLA and surgery respectively (p=0.0617). At 4 and 16 weeks, 100% of patients in both groups had complete eradication of reflux. This highlights that whilst some residual reflux may be detectable initially, evolution of the ablative changes continues for an extended period.

Christenson et al[362] reported a RCT of EVLA (980nm 10-12W, pulsed mode) versus surgery. Concomitant phlebectomies and perforator ligations were performed in both groups where indicated. There was 100% technical success in both groups (abolition of flow in EVLA patients, and absence of vein in surgical patients) at 6 hours and 12 days but at 2-year follow-up there were significantly more EVLA patients (8) than surgery patients (2) with detectable GSV reflux (p=0.05). Additionally, two EVLA patients were identified to have completely open GSVs at 1 year; they underwent HTSA and were excluded from further analyses. Neovascularisation was not commented upon.

There are a number of methodological limitations to this study that reduce its applicability to standard EVLA practice in the NHS. The inclusion criteria stated a maximum GSV diameter of 15mm at 3cm from the SFJ. Four patients randomized to the EVLA group were excluded due to vasospasm preventing GSV access; the authors only undertook per protocol, rather than intention-to-treat (ITT) analyses. GSV stripping in the surgery group was to the knee or ankle, depending on the extent of reflux. As discussed earlier, the accepted practice is to strip to the knee-level only. All patients in both groups received either general or spinal anaesthesia. Despite being a RCT, the baseline clinical severity was significantly different between the groups,

with a greater propensity of C4 disease in the surgery group (18 versus 7, p=0.031). A recent Cochrane review[278] highlighted that legs, rather than patients, were randomized in this study. Bilateral procedures were performed in 40 patients in this study, 8 of whom underwent EVLA to one leg and surgery to the other[366].

Pronk *et al*[364] performed a RCT of EVLA (980nm 12W continuous mode) versus SFJ ligation and GSV stripping. Both procedures were performed under tumescent anaesthesia and all patients received liquid sclerotherapy of varicosities. Target LEED in the EVLA group was reduced in proportion to GSV diameter and distance from the SFJ; mean (SD) LEED was 64.5Jcm$^{-1}$. The primary outcome measure was DUS-detected recurrence of varicose veins at 10 years. This one-year interim analysis focused primarily on QoL and pain (see below). In terms of recurrence at one year, no significant differences in the development of recurrent varicose veins were seen between EVLA (10%) and surgery (9%).

### *Clinical Outcomes and Complications*

Rasmussen *et al*[358] reported significant intragroup improvement in VCSS scores for all EVLA patients at 3 months and two years[253] over baseline, with no statistical intergroup difference between EVLA and surgery. The studies by Darwood *et al*[359] (3 months and 1 year follow-up) and Christenson *et al*[362] ( 1- and 2-year follow-up) reported similar findings.

The Pronk *et al*[364] study reported similar improvements in clinical symptoms for both EVLA and surgery groups at one year, as well as significant improvements in CEAP classification. However, no validated score such as VCSS was included and, as discussed earlier (see CEAP, p.32), the CEAP system is neither dynamic nor responsive enough to be used as an assessment of improvement following treatment.

In addition to CIVIQ scores, the study by Kalteis *et al*[361] had a second primary outcome measure of "haematoma" size in the medial thigh at one week; their definition of haematoma also included bruising, and was measured by tracing the area onto transparent acetate. Median (IQR) area of bruising was 125cm$^2$ (5-180cm$^2$) and 200cm$^2$ (123-269cm$^2$) in the EVLA and surgery groups respectively (p=0.001). The overall number of patients affected by "haematoma" was significantly different between the 2 groups, 34% of EVLA and 58.3% and surgery patients respectively

(p=0.024). 12% of the EVLA group and 10% of the surgery group still had residual "haematoma" at 16 weeks (p>0.999).

An early study of 810nm EVLA versus surgery failed to show any difference in pain scores between the two groups, but did reveal significantly less bruising and oedema after EVLA[367]. However, the study has some significant methodological limitations. Each patient underwent a bilateral procedure, with one leg randomized to EVLA and the other to surgery; any analyses of pain would therefore not be expected to show a significant difference between the modalities. The EVLA leg also underwent SFJ ligation prior to laser ablation, which is currently considered an unnecessary intervention, and may have added to the pain associated with EVLA. All patients were operated on under spinal or epidural anaesthesia, and the EVLA legs did not receive tumescent anaesthesia.

There were no statistically significant differences in pain scores or analgesia use in the either the Darwood et al[359] or Christenson et al[362] studies.

The Rasmussen RCT[358] found a significant difference between patient-reported pain scores over the first 10 days in favour of EVLA (p<0.01), although the method of comparison is not clear. The investigators used intravenous sedation for the majority of procedures in addition to tumescent anaesthesia for both procedures. It is not known whether this practice, which is not directly applicable to the standard practices within the NHS, could potentially influence pain perception and early QoL.

Kalteis et al showed no differences in 10cm VAS pain scores or analgesia usage. However, they did demonstrate significantly lower "discomfort ratings" for paraesthesia with EVLA than with surgery over the first two (p=0.009) and up to seven (p=0.022) postoperative days, despite no tumescent anaesthesia being used.

Mean (SD) periprocedural VAS pain scores in the study by Pronk et al[364] were significantly higher in the surgery group (3.39 [2.57]) than the EVLA group (2.21 [2.40]), p=0.02. However, the pain score at day 7 (p < 0.01), day 10 (p < 0.01) and day 14 (p=0.01) was significantly higher after EVLA (Table 2).

Major complications following EVLA are rare, with studies reporting rates of DVT, paraesthesia and skin burns at around 1%, 2% and 0.4% respectively[368]. Pain, bruising and haematoma and phlebitis are common side effects associated with EVLA, but in

most cases are self-limiting and short-lived. The Rasmussen RCT[358] showed EVLA to be safe; rates of phlebitis, haematoma and bruising were 3%, 5% and 11% respectively at 12-day follow-up, while there were no cases of infection and only one case (2%) of paraesthesia reported at 1-month follow-up. All complications had resolved by 3 months. No statistical comparisons were made with the conventional surgery group, but they appear broadly similar. Other case reports have described various complications such as arteriovenous fistulae[369,370], and an isolated CVA in a patient with a PFO[371].

### QoL

The changes to QoL measured in these studies appear mixed. All appear to show overall benefit over baseline at varying time-points between 3 months and 2 years.

Rasmussen *et al*[358] reported significant SF36 improvements in both EVLA and surgery groups over baseline scores at 3 months. There was a significant reduction (deterioration) in scores for physical functioning (PF), role-physical (RP) and bodily pain (BP) in both groups at 12 days. There was no direct statistical comparison between the EVLA and surgery groups at this time period.

In a similar fashion to SF36, the AVVQ scores in the Danish study were significantly worse at 12-day follow-up in comparison to baseline. However, scores had returned to baseline by 1 month and were significantly improved over baseline in both groups by 3 months, with no intergroup differences. At two-year follow-up[253], the improvements in QoL were maintained, still with no intergroup differences.

The values for AVVQ, VCSS and SF36 in this study were reported as means; it is likely that these data were not normally distributed and hence median values and comparison by non-parametric tests would have been more appropriate.

Similar results were reported in the RCT by Christenson *et al*, where significant improvements in SF36 physical domains over baseline were shown for both EVLA and HTSA at one-year follow-up. These improvements were maintained to 2 years with no intergroup differences at any time point[362]. The most marked improvements over baseline in both groups were in the BP, PF and VT domains. QoL at the initial 12-day follow-up was not reported, however, so it is not clear whether there were any postoperative differences.

The three-arm study by Darwood *et al*[359] reported equal significant improvements in AVVQ scores at 3 months over baseline, and maintained to one year. However, insufficient patients were included to meet their original power calculation.

Using the CIVIQ score, Kalteis *et al* found no intergroup differences in QoL at 4-week follow-up between the EVLA and surgery[361]. However, while the authors recruited the required 50 patients per group stipulated in the power calculation, the study was ultimately underpowered due to losses to follow-up and a *per protocol* analysis.

In the Pronk *et* al study[364], individual reporting of EQ5D domains identified that patients treated with EVLA were significantly less mobile at 7 ($p<0.01$) and 10 ($p=0.01$) days, and that they experienced significantly more hindrance in their daily activity ($p=0.01$) and self care at day 7 ($p=0.03$). However, the EQ5D was not designed or validated for reporting on an individual domain level in this way, and therefore these findings should be interpreted with caution. Furthermore, these findings did not equate to any differences between the groups in terms of time to resume normal daily activities, return to work or sporting activities. Neither overall EQ5D utility index nor VAS ratings were reported in the study.


## EVLA versus RFA

As discussed earlier, there were no RCT data for newer RFA devices versus the gold-standard of conventional surgery at the time of commencing this MD. However, a small number of RCTs comparing EVLA and RFA devices had recently been reported[336,372-374]. Technical efficacy appeared equivalent with the newer RFA devices, but there was some modest evidence that RFA resulted in less postoperative pain.

A RCT of ClosurePLUS versus EVLA (810nm 14W continuous mode)[372] revealed significantly lower postoperative pain scores with RFA, however at one year there was a significantly increased rate of recanalization compared to EVLA (11 versus 2 limbs, $p=0.002$). Clinical recurrence rates were not reported. Mean (SD) LEED in the EVLA group was 92 (14.2) $Jcm^{-1}$. Patients in the EVLA group underwent more extensive phlebectomy. There were no differences in QoL between the groups (measured using CIVIQ-2) at one month or one year; both improved significantly over baseline.

Clearly this study was based on outdated RFA technology and therefore it is not directly applicable now.

Shepherd et al[373] published a RCT of ClosureFast™ versus 980nm EVLA. The primary outcome measure of the study was pain over the first 3 days but unfortunately there was no report of technical success or other DUS outcomes. Both procedures were performed under GA, which negates some of the benefits of an endovenous approach under LA, and is not representative of current practice. Tumescent anaesthesia was used in addition to GA, but clearly the infiltration may not have been as diligent given that patients were under GA and hence perioperative pain was not a concern. After adjustment for baseline variables and analgesic use in this study, there was no statistically significant difference between RFA and EVLA. Furthermore, the reported pain scores had no bearing on return to normal function. Complications were low, with no differences between the groups. In terms of QoL, intragroup AVVQ and SF12 scores all significantly improved from baseline to 6 weeks, but there were no intergroup differences. VCSS results also displayed significant intragroup improvements over baseline for both ClosureFast™ and EVLA, with no significant intergroup differences.

The RECOVERY study[374], funded by VNUS Medical Technologies, randomized 87 limbs in 69 patients to undergo either ClosureFAST or EVLA (980nm, 12W continuous mode). Phlebectomy was deferred in both groups until at least 30 days; the authors did not report the rates of secondary intervention. The primary outcome measure was postoperative pain measured by 10cm VAS. Other outcomes included complications, ecchymosis rated by clinical staff on a 0-5 scale, patient-reported tenderness and QoL measured using CIVIQ-2 at 48 hours, 1, 2 and 4 weeks. The ClosureFAST group reported significantly lower (mean [SD]) 10cm VAS pain levels than the EVLA group during visits at 48 hours (0.7 [0.9] versus 1.9 [1.6]), 1 week (0.2 [0.6] versus 1.8 [1.8]), and 2 weeks (0.1 [0.4] versus 1.2 [1.7]), all p values <0.0001. There were no differences at one month. The authors also reported significantly lower scores for postoperative tenderness, ecchymosis ratings, VCSS at each time-point over the first two weeks. Tumescent anaesthesia was used in both groups, containing 0.1% lidocaine with epinephrine. Volumes administered were not reported. It would have been interesting to know the perioperative pain scores for both groups. Follow-up was short, up to 30 days, and therefore durability of closure cannot be commented upon, although the authors report 100% closure rates in both groups at 30 days. The

magnitude of energy delivery was not reported. While the LEED in RFA is largely fixed, and can therefore be surmised, this is not the case with EVLA. A combination of less tumescent anaesthesia with significantly higher LEED in the EVLA group may have accounted for the observed differences in a study funded and supported by the manufacturers of the RFA device.

One small RCT of RFiTT versus 810nm EVLA has been reported[336]. Patients were stratified into either bilateral or unilateral disease. Those with bilateral disease were randomized to receive one of the treatments to the right leg, with the left leg receiving the other treatment modality. Patients in the unilateral arm were randomized to receive either one or the other treatment. This study did not routinely use tumescent anaesthesia for the RFiTT group, and all procedures were performed under GA. The EVLA group did receive tumescent fluid (0.9% NaCl), without addition of local anaesthesia or epinephrine. In terms of pain scores, there were some interesting findings. Patients in the bilateral arm of the study reported significantly higher 10cm VAS pain scores in the EVLA leg compared to the RFiTT leg at days 2 to 11 (reported in graphical form, p value not given). However, in the unilateral arm, there were no differences between the two treatments.

In terms of technical success, the results were generally disappointing in comparison to other studies, with occlusion rates of 78% and 74% for EVLA and RFiTT respectively at 9 months. There were no differences in AVVQ scores between the two treatments at 6 months.

In a short letter, the same research group[375] refers to a study of RFiTT™ versus ClosureFast™ in 11 patients with bilateral GSV reflux. Under GA, each patient underwent RFiTT™ to one leg and ClosureFast™ to the other. At one-year follow-up (numbers attending not declared) there were no recurrent varicosities. All the GSVs examined in the ClosureFast™ group remained occluded, while one GSV in the RFiTT group displayed reflux. The authors claim equivalent outcomes, but clearly this study is fundamentally flawed, being seriously underpowered to show any significant difference, with incomplete reporting of baseline characteristics.

## EVLA versus UGFS

A non-randomised study of 98 patients undergoing either UGFS (3% polidocanol, 1:4 sclerosant to air ratio using Tessari technique) or EVLA (980nm, 15W continuous mode)[376] reported a significant advantage of EVLA in terms of one year occlusion rates (93.4% versus 77.4%, p=0.0465) and rates of reflux (2.2% versus 15.1%, p=0.036). UGFS also appears to be influenced more by preoperative GSV diameter, with logistic regression suggesting 90% treatment success for UGFS of veins <6.5mm, whereas the same success rates were predicted in the EVLA group up to 12mm diameter.

## The CLASS Trial

The CLASS (Comparison of LAser, Sclerotherapy and Surgery) trial was actively recruiting participants at the commencement of this MD. This multicentre NIHR HTA programme-funded RCT aims to identify superiority between the three techniques in terms of clinical and cost-effectivness. Recruitment is now closed and the results are greatly anticipated.

## Hull Endovenous Laser Project 1; HELP-1

A RCT of EVLA (810nm, 14W continuous mode with AP) versus conventional surgery from this unit completed recruitment in late 2009; the short-term results (up to one year) were being analysed during the early phase of this MD thesis, and published recently[274,377]. Whilst this study was not the first trial to compare the two modalities, it was the first specifically powered to investigate the differences in QoL, rather than safety and technical success, which had already been reported by other RCTs and many non-randomised reports, as discussed above.

The primary outcome measure was QoL measured using the generic SF36 instrument. The study was powered to find a medium-sized difference between EVLA and surgery in the physical domains of SF36, based on an earlier pilot study[273]. Secondary outcome measures were: -
- QoL measured by EQ5D and AVVQ
- Clinical recurrence rates

- VCSS
- Post-procedure pain
- Complication rates
- Return to activities
- Patient satisfaction with cosmesis and overall treatment
- Technical success and recurrence rates on DUS

There are several salient findings from this study. In terms of the primary outcome measure, as other studies have previously shown[358] there was a worsening of QoL scores one week after surgery, with relatively preserved scores in patients undergoing EVLA compared to surgery[378]. After 1 week, the Surgical group demonstrated significant deterioration in five of the eight SF36 domains: Physical Functioning (p<0.001), Role-physical (p<0.001), Bodily Pain (p<0.001), Social Functioning (p=0.001) and Role-emotional (p=0.029). EVLA caused significant deterioration in only two domains: Physical functioning (p=0.018) and Role-physical (p<0.001); preoperative scores in the domains of Bodily Pain, Social Functioning and Role-emotional were preserved.

Intragroup analysis of EQ5D and AVVQ demonstrated significant deterioration in both groups at one week, followed by significant improvements over baseline at 12 and 52 weeks. There were no significant intergroup differences at any time point.

On intention to treat analysis, technical success, defined as abolition of flow on DUS, was higher after EVLA (136 of 137 patients [99.3%]) than surgery (122 of 132 patients [92.4%]), p=0.005. The single technical failure in the EVLA group was due to inability to achieve GSV access, while in the Surgery group it was due to vein snapping during stripping (6 of 10), failed groin dissection in patients previously abusing intravenous drugs (2 of 10) and groin tributaries emanating from the posterior CFV that could not be dealt with safely within the context of a standard groin dissection (2 of 10).

Patients undergoing EVLA reported significantly lower VAS pain scores and correspondingly significantly less analgesia usage over the first postoperative week in comparison with the surgical group.

The surgery group took longer to return to normal activities, with an overall median (iqr) of 14 (7–25) versus 3 (1–10) days p<0.001 and, in employed individuals, to return to work (14 [13–28] versus 4 [2–14] days, p<0.001).

Complication rates were low, however surgical patients suffered more sensory disturbance (9.8% versus 2.9%, p=0.02), haematoma (8.3% versus 0.7%, p=0.003) and infection (6.0% versus 1.5%, p=0.048) than EVLA patients.

Clinical recurrence at one-year follow-up was significantly higher in the Surgery group (20.4%) compared with EVLA (4.0%), p<0.001.

Clinical severity, measured by VCSS, significantly improved over one-year follow-up in both groups, from a median (iqr) of 4 (3–5) at baseline to 1 (0–1) by 3 months (p<0.001). The improvements were maintained in both groups at 1 year, with no difference between groups at any time point.

## Tumescent-less Ablative Techniques

Given that infiltration of tumescent anaesthesia appears to account for the majority of periprocedural pain during EVTA procedures, attention has turned in some quarters to other ablative techniques that do not use thermal energy and hence do not require tumescent anaesthesia. The relative merits and limitations of UGFS have been discussed earlier (see Ultrasound-guided Foam Sclerotherapy, p.79). Additionally, since the commencement of this MD thesis, two further techniques have entered experimental clinical practice.

### *Mechanochemical Ablation*

This technique combines liquid sclerotherapy with mechanical abrasion of the venous endothelium, based on the hypothesis that this will create a more successful long-term ablation than UGFS alone.

The ClariVein® (Vascular Insights, Madison, Connecticut, USA) device is comprised of an infusion catheter, which encompasses a wire that rotates at approximately 3000rpm[480], in order to both disperse the liquid sclerosant (typically STD or polidocanol) and create endothelial damage as the catheter is withdrawn. There

have been no prospective comparative studies of this technology in the treatment of GSV insufficiency. However, two small case series reported by the same group, have quoted occlusion rates of 87% to 94% at follow-up of between 6 weeks and 8.5 months[480,481]. Complication rates appear high, with 21% and 26% of patients having superficial thrombophlebitis and haematoma, respectively[480]. These rates are significantly higher than the complications with either EVLA or surgery in this thesis or other contemporary studies.

A study of ClariVein for SSV reflux, also by the same group, reported median (iqr) peri-procedural VAS pain of 2 (2-4). There was a 14% rate of superficial thrombophlebitis[482]. There was no assessment of post-procedural pain or QoL.

### *VenaSeal Sapheon Closure*

This procedure uses catheter-delivered cyanoacrylate adhesive under ultrasound guidance. Cyanoacrylate adhesive has been used extensively in other clinical settings such as wound repair, haemostasis in bleeding upper gastrointestinal varices and ulcers, embolization of varicocele and AVM, and treatment of type I and II endoleak after EVAR[483-485]. A proof-of-concept study of cyanoacrylate venous ablation in a live swine model was reported in 2012[486], with the same author group reporting a first-in-human study shortly after[487]. This revealed a 92% occlusion rate at 12 months, while 6 of the 38 patients (15.8%) developed superficial thrombophlebitis.

The procedure is yet to gain FDA approval in the USA, and is only provided by a small number of surgeons in the UK and Europe. Long-term clinical efficacy and safety data are not yet available to support widespread adoption, nor are there any comparative studies with the more established ablative techniques.

In summary, therefore, approximately a decade after mainstream introduction of EVTA, both RFA (ClosureFAST/Venefit) and EVLA are shown to be at least as safe and have similar short-term efficacy as surgery, with some subtle short-term advantages. EVTA techniques also appear to have a lower proclivity than open surgery to invoke groin neovascularization[339,342,379-381], which may in turn reduce long-term recurrence rates.

Following this evidence, surveys have shown an increased use of endovenous treatment options in the NHS[382,383]. Separate treatment codes for UGFS, RFA and EVLA have been in use by the Hospital Episode Statistics (HES) recording of treatments for SVI since 2006. Slightly bucking the evidence base thus far, these data have shown that the most commonly used endovenous treatment is UGFS, with EVLA being the most frequently used thermal ablative procedure. Notwithstanding the increase in endovenous therapy, however, over 70% of patients undergoing treatment for SVI in the NHS still receive conventional surgery[384], although the gap appears to be closing rapidly.

In addition to confirming the technical and clinical efficacy of these procedures over the longer term, current focus is turning to optimization of technique, patient selection and choice of adjuvant procedures to further improve patient outcomes.

## Optimising the EVLA technique

While a standard protocol is in common use for ClosureFAST RFA, EVLA protocols have been extremely variable because of the diversity of the equipment from a range of manufacturers. Some of these issues are being addressed by inter-society consensus statements and guidelines for the use of EVLA[146,332]. Modifications in the technique have the potential to further optimize the procedure in terms of clinical efficacy and patient outcomes. However, the ClosureFAST technique is essentially not operator-modifiable, offering an "off-the-shelf" treatment; other than for the generally accepted practice of applying a double-treatment cycle to the proximal GSV segment, ClosureFAST RFA does not offer any further option for variation in technique. Conversely, the EVLA technique has numerous variables that can be adjusted and therefore offers more potential for improvement of technique and consequently patient outcomes.

### Tumescent anaesthesia

A major key to the success of EVTA appears to be the use of tumescent anaesthesia. As described above, early attempts at thermal ablation that did not use tumescent anaesthesia reported significant complications. The methods changed rapidly,

resulting in reducing damage to perivenous tissue through the application of tumescent anesthesia, initially developed within the field of plastic surgery and liposuction[385]. This further minimized adverse sequelae in addition to making the procedure better tolerated by patients. In 2004, Zikorus and Mirizzi demonstrated a significant reduction in temperatures at the venous adventitia with the addition of a tumescent anaesthesia layer[386]. Given that the superficial veins are intimately associated with superficial nerves, this appears to reduce the risk of neurological sequelae; Merchant *et al* demonstrated a significant reduction in the incidence of paraesthesia after the introduction of tumescent anesthesia to the RFA procedure, from 14.5% to 9.1%[387]. In the longer term, the incidence of paresthesia decreased to 6.7% at 6 months and 2% at 4 years with the use of tumescent anesthesia. Data from the authors' clinical registry also showed a significant reduction in skin burns from 1.8% before to 0.5% after introduction of tumescent anaesthesia[387].

Constituents of this tumescent anaesthetic solution vary between institutions; published reports of endovenous thermal ablative techniques typically fail to report the specific formulation used, or the volume infused.

In essence, the tumescent solution typically includes a commercially available crystalloid fluid for intravenous infusion, to which various local anaesthetics, with or without epinephrine, can be added. Epinephrine promotes vasoconstriction of the vein and should be used to reduce the incidence of haematoma and hyperpigmentation[388], in addition to delaying the absorption of local anaesthetic, thus prolonging its effects. Further options for the tumescent solution include warmed versus cold solutions.

Anecdotally, the most painful part of EVTA procedures appears to be the infiltration of tumescent anaesthesia; other authors have also reported this finding[364,389]. Patients appear to experience less pain with the manufacturer-recommended tumescent anaesthesia solution used as part of the ClosureFAST procedure, compared with the standard solution typically used in EVLA. The key difference between the two preparations, which are made by the operating team prior to each case, is the addition of sodium bicarbonate in the ClosureFAST-recommended solution. The principle behind this is to buffer the solution towards a more physiological pH, from the baseline acidic pH. Although the use of sodium bicarbonate to buffer local anaesthetic is technically "off-label", the practice is supported worldwide by a wealth of literature[390-393].

A previous Cochrane review[394] revealed that adjustment of the pH of lidocaine solutions by the addition of sodium bicarbonate results in a significant reduction in patient-reported pain on a 10cm VAS during skin infiltration. This effect was greater with solutions containing epinephrine than plain lidocaine. There are currently no reports in the literature to provide any evidence-base for this practice within the context of tumescent anaesthesia for EVTA. However, it is intriguing that perhaps perioperative pain can be reduced by a relatively simple (and inexpensive) addition.

The EVTA technique mandates that local anaesthesia be used for both skin infiltration (as per the Cochrane review) and additionally for perivenous tumescence. It is possible, therefore, that the beneficial effects of a buffered solution could be even greater in this patient population than in those previously studied. It is conceivable that a reduction in periprocedural pain may result in lower postprocedural pain scores and improved short-term QoL. This is a significant factor, given that the NHS PROMs project will use 6-month QoL data to calculate QALYs, which ultimately may then be used to commission services.

### *Concomitant or delayed treatment of varicosities?*

It is generally believed that reflux in truncal veins must be treated before addressing any visible abnormalities. The "descending" theory of SVI pathogenesis suggests that treatment of an incompetent trunk would ultimately reduce the degree of reflux in varicose tributaries. In keeping with this idea, some surgeons elect to defer treatment of varicosities until after assessment at a later date, arguing that the extent of delayed treatment is less than if undertaken concomitantly[332]. However, data from RCTs and large case series have not borne out this opinion.

In an early prospective study of patients with GSV insufficiency undergoing truncal RFA alone, only 13% of visible varicosities underwent complete resolution and only 41% had no further treatment[395]. Two further early retrospective case series of RFA (ClosurePLUS) reported overall requirements for secondary procedures (either AP or sclerotherapy) of 36% and 61% at 8-month[396] and 3-year follow-up[397], respectively. Broadly similar results were quoted in a case series of patients undergoing EVLA

alone[398]. No assessments of pre- or postoperative clinical severity or QoL were made in any of these reports.

A previous RCT from this unit compared EVLA alone with EVLA plus concomitant AP[399]. The requirement for subsequent interventions assessed at 6 weeks was reduced from 67% in the control group to 4% in the AP group (p<0.001). At 3 months, the EVLA plus AP group had significantly better VCSS scores than EVLA alone (median [iqr] 0 [0-1] versus 2 [0-2], p<0.001). There were no differences in the low complication rates, postoperative pain scores or time to resume normal activity between the groups. Disease-specific AVVQ scores were also significantly better in the EVLA plus AP group at both 6 (p<0.001) and 12 weeks (p=0.015).

Assessment of data between studies that performed EVLA alone, or in combination with concomitant treatment, but without direct comparison of the two approaches, is difficult due to heterogeneity in study design. The RCTs performed by Kalteis *et al*[361] and Rasmussen *et al*[358] discussed earlier both included concomitant AP. The rates of reintervention were not quoted. In both studies, it is suggested that the AP may have contributed significantly to the postprocedural pain.

In the RCT of EVLA alone versus cryostripping[360], 62% of patients in the EVLA group had clinically apparent varicosities at 6 weeks; all underwent liquid sclerotherapy. In the RCT by Darwood et al[359], delayed injection sclerotherapy to varicosities was performed at 6 weeks, if requested by the patient. 46% of patients requested sclerotherapy, with 10% undergoing more than one session. It is not clear how significant any residual varicosities were in the patients not undergoing sclerotherapy, whether they would have further benefitted from a concomitant procedure, and what the long-term sequelae of untreated varicosities are. What is known, however, is that secondary procedures are unpopular with patients, with 71% wanting full treatment of their varicose veins in a single visit[383]. A one-stop single treatment seems attractive to both patients and surgeons alike[373,400].

A more cynical view of the decision to defer adjuvant treatment of varicosities is that it may increase revenue for the treatment-provider, depending on funding arrangements with the payer.

Based on the "ascending theory" of SVI pathogenesis, a truncal only approach may leave large reservoirs of untreated reflux in the varicosities, from which recanalization of the main axial vessel may occur, even if the varicosities are reduced in size and not clinically evident.

### *Ambulatory Phlebectomy or Sclerotherapy for varicosities?*

Adjuvant treatment of varicosities after EVTA typically involves either ambulatory phlebectomy under tumescent anaesthesia, injection sclerotherapy or UGFS. Out of these options, there have been no comparative studies in the context of EVTA.

De Roos *et al*[401] performed a RCT of AP versus injection (liquid) sclerotherapy for the treatment of isolated anterior thigh circumflex vein varicosities. A total of 98 legs in 82 participants were randomised equally; 49 legs received liquid sclerotherapy and 49 received AP under local anaesthesia. 16 participants underwent bilateral procedures, but the authors did not report whether both legs received the same treatment or not. Participants were followed up for two years. The outcome measures were recurrence and complication rates.

Recurrence rates at 1 year were 25.0% versus 2.1% (statistical analysis not reported) for the sclerotherapy and AP groups respectively. At 2-year follow-up recurrences were noted in 36.7% of the sclerotherapy group, but no further cases in the AP group, giving an overall risk ratio (RR) of 18.0 (95% confidence interval 2.5 to 129.35) in favour of AP. It should be noted, however, that this study used liquid sclerotherapy; as discussed earlier, the failure and recurrence rates of liquid are typically inferior to the newer technique of UGFS.

In terms of complications, it should be noted that the occurrence of telangiectatic matting at 2 years was significantly higher following phlebectomy. The sclerotherapy group had a higher incidence of phlebitis (27% versus 12%), but this did not reach statistical significance (p=0.07). There were no differences in the rate of haematoma. This study reported blistering in 31% of the AP arm, which is significantly higher than reported in other large series of AP. A review of 1000 consecutive cases of AP[402] identified a very low complication rate; the most frequently encountered complications were minor: blister formation (1.3%), phlebitis (1.1%), telangiectasias (0.5%),

hyperpigmentation (0.4%) and temporary sensory nerve damage (0.2%). Hence, AP in experienced hands is a low-risk procedure.

In the VEDICO trial discussed earlier, combined treatment failures and losses to follow-up analysed by ITT were 41% in the AP group, compared with 20% in the UGFS group (p< 0.02)[325]. However, clearly this study is not representative of the treatment scenario in which the options are being discussed in the present context; when used as the primary treatment, UGFS will treat both truncal and varicosity reflux, whereas AP will not address truncal reflux.

### *Delivery of endovenous laser energy*

The dose of laser energy delivered can be changed, either by altering the power settings (Wattage) on the generator unit, or by changing the speed of catheter withdrawal. Work from this unit has shown a reduction of DUS-detected recurrence at the SFJ, and improved patient satisfaction with cosmesis with 14W versus 12W 810nm EVLA[403].

Energy delivery is expressed in terms of linear endovenous energy density (LEED), the amount of energy delivered per unit length of vein treated, typically in joules per cm ($Jcm^{-1}$), or as endovenous fluence equivalent (EFE), which is laser energy delivered to a cylindrical approximation of the vein based on luminal diameter ($Jcm^{-2}$).

Data on energy delivery in EVTA first began to emerge in 2004[404], with an apparent dose-response relationship between the amount of energy deposited into the vein and the durability of ablation. Using the 810nm laser, optimum occlusion rates appear to be achieved with a minimum LEED of 60 $Jcm^{-1}$ [347,405,406]; lower LEED has been shown to correlate with vein recanalization. However, a sufficiently high LEED / EFE alone does not appear to be the sole determinant of technical success; in a prospective study, 9% of veins successfully treated with LEED exceeding 80 $Jcm^{-1}$ had unexpectedly recanalized at 6-month follow-up[407].

Endovenous laser energy is delivered from the tip of an optical fibre, and is highly focused, with temperatures well over 100°C[408]. As a result of the high temperature and the focused nature of the laser beam, EVLA at the lower wavelengths (810-980nm), unlike RFA, is generally associated with vein wall perforations[408]. It is

surmised that these perforations, with extravasation of blood into the surrounding tissues, is responsible for much of the pain associated with EVLA. An *ex vivo* histological study of bovine hindfoot venous segments treated with ClosureFast™ demonstrated homogeneous intimal and medial thermal ablation and disintegration. This differed from veins treated with EVLA, where major perivenous tissue ablation and vein wall perforations were present[409]. However, this study is fundamentally flawed in that perivenous tumescent techniques were not utilized and the animals were not live. Work from this unit suggests that with diligent tumescent anaesthesia infiltration, an increase in LEED does not increase patient morbidity or complication rates[410].

It is clear, however, that there is a balance to be achieved between optimum venous occlusion rates, and incidence of perivenous damage with its subsequent complications and increased pain.

Lower LEED / EFE may be achievable with water-specific laser wavelengths (1320 nm to 1500 nm) which target the vein wall rather than endoluminal blood, as they have greater tissue penetration whilst delivering equivalent technical efficacy, without the localized perforations associated with the older technology. Higher wavelength EVLA has been shown to result in vein wall collagen formation, venous spasm and minimal thrombosis[411]. It is yet to be proven, however, whether these differences in EVLA wavelength translate into real-life benefits in terms of patient outcomes.

In addition to wavelength and power settings, the delivery of endovenous laser energy may be modified by the type of optical fibre tip employed. Early devices used a simple bare-tip, which has also been implicated in the occurrence of vein wall perforations, charring and consequent pain. However, as technology has evolved, there have been developments aimed at reducing fibre tip contact with the vein wall. These developments have seen the introduction of a 'jacket' to cover the bare tip (the jacket-tip fibre) as well as glass, ceramic, diffusion, radial-firing and tulip-tipped fibres. These are thought to result in a more uniform transfer of energy to the vein wall, and therefore less vein wall perforation. Jacketed fibre tips, which are in most common usage, use a shrouded tip covering, typically gold, to create a slightly divergent laser beam, rather than the standard forward-firing bare-tipped fibre. This theoretically directs the laser energy into the vein wall, without the focal targeting implicated in wall perforation.

In the short-term follow up of an RCT of 810nm EVLA using a bare-tip fibre versus 1470nm EVLA using a radial-firing fibre, the latter combination was shown to reduce postoperative pain and bruising[412]. However, some evidence of more treatment failures has been reported[413]. Data on the efficacy of other fibre tip designs were not available at the commencement of this MD.

## 1.5 Aims and Objectives

At the commencement of this programme of research, endovenous thermal ablation had emerged as a contender for a new "gold-standard" in the treatment of SVI. However, this assertion was based primarily on early non-randomised studies and a handful of RCTs with heterogeneous methodology reporting short-term outcomes. Within this treatment modality, EVLA appeared to have the most convincing evidence base, with scope for technique modification and improvement. The one-year QoL, clinical and DUS outcomes from this unit's RCT of EVLA versus conventional surgery (HELP-1) were in the process of being analysed and subsequently published[377,378]; they added further support to adopting EVLA as the treatment of choice for SVI.

Based on these early outcomes, it appeared that the objectives for future work on the treatment of SVI should be twofold:-

1) To continue longer term follow-up of EVLA outcomes in comparison to the present gold-standard of conventional surgery

2) To identify areas of the EVLA treatment modality that could be manipulated or optimized to further improve patient outcomes.

In order to investigate these objectives, five studies were envisaged.

### Study 1: Two-year clinical, QoL and DUS outcomes from the HELP-1 RCT

As discussed above, the one-year outcomes from a RCT of EVLA versus conventional surgery in the treatment of SVI demonstrated a convincing case for EVLA to challenge for position as a new "gold-standard" in the short-term. However, longer-term follow-up is required to confirm maintenance of these outcomes.

This study aimed to undertake analyses of the 2-year outcomes from the HELP-1 RCT. In addition to assessment of the initial primary outcome measure of QoL, it was felt important to undertake an in-depth analysis of clinical and DUS recurrence rates and their characteristics in order to inform how the EVLA technique might be further optimized.

## Study 2: Buffering of Tumescent anaesthesia: finding the optimum solution

Some anecdotal evidence suggested that buffering of tumescent anaesthesia solutions to a physiological pH may result in reduced pain on infiltration. Given that tumescent anaesthesia is key to the success of EVLA, this sparked a real interest. The first objective was to ascertain what was the optimal solution in terms of achieving a physiological pH, which could then be taken forward and tested in clinical practice.

## Study 3: Cohort study of Buffered versus unbuffered tumescent anaesthesia

Having ascertained the optimal solution for a physiological pH in Study 2, this was tested in a cohort study of patients undergoing routine EVLA with AP. The aim of this non-randomised pilot study was to gain data that could be used in a power calculation for an RCT of buffered versus unbuffered tumescent anaesthesia.

## Study 4: Prospective cohort study of concomitant phlebectomy or sclerotherapy of varicosities

Evidence lends support to a policy of undertaking concomitant treatment of varicosities during EVLA. However, there is a paucity of evidence to base any decisions on whether varicosities are better treated with AP or sclerotherapy. This non-randomised study sought to gain an idea of the benefits of both adjuvant techniques in terms of clinical, QoL and DUS outcomes.

## Study 5: Prospective cohort study of 810nm versus 1470nm EVLA

As discussed earlier, there has been some early evidence that EVLA with longer wavelengths may offer superior short-term patient outcomes. However, no comparative studies between 810nm and 1470nm existed at the onset of this research programme, particularly focusing on QoL. This study aimed to assess whether a 1470nm wavelength can make a difference to short-term clinical, QoL and DUS outcomes in comparison to the more traditionally used 810nm technology.

# Chapter 2: Methods

## 2.1: Study 1: Two-year clinical, QoL and DUS outcomes from the HELP-1 RCT

### 2.1.1 Participants

All participants in the Hull Endovenous Laser Project -1 (HELP-1) RCT of EVLA versus surgery (www.clinicaltrials.gov NCT00759434) were invited to attend their scheduled two-year follow-up appointment. The initial trial methodology has previously been reported[377,378]. In brief, consecutive patients with unilateral primary, symptomatic SFJ and GSV insufficiency were randomized to undergo either conventional surgery under GA or EVLA (810nm, 14W continuous mode) with concomitant AP under tumescent anaesthesia.

### 2.1.2 Procedural Techniques

*Conventional Surgery*

Surgery was performed under GA. The procedure followed standard convention, as described earlier (see 1.4.3 Conventional Surgery, p.64)

*EVLA*

Patients deemed to be at high risk of VTE, using the standardised trust pre-operative risk-assessment proforma, received a single pre-operative dose of prophylactic low molecular weight heparin (LMWH), as per standard NHS practice.

Patients underwent pre-operative DUS assessment using a portable MicroMaxx® ultrasound system (Sonosite Ltd, Hichin, UK). DUS-guided marking with a permanent skin marker pen was performed by the operating surgeon to identify the Saphenofemoral Junction (SFJ), the course of the GSV, and varicosities to undergo AP.

The patient was then positioned on the operating table and underwent sterilization of the leg to be treated using 7.5% Povidone-Iodine (Videne®, Ecolab Ltd, Leeds, UK); patients with an iodine allergy received 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep®, Insight Health Ltd, Wembley, UK). Sterile draping was subsequently performed in the standard fashion.

With the patient in the reverse Trendelenburg position to enhance venous filling, the GSV was cannulated under ultrasound guidance after administration of local anaesthesia using 1% Lidocaine with 1:200,000 epinephrine (Xylocaine, AstraZeneca UK Ltd, Luton, UK). The initial aim was to cannulate the perigenicular GSV, thus treating the same length of GSV as in the conventional surgery group; the technique evolved towards the latter end of the trial, to ultimately perform cannulation at the lowest point of demonstrable reflux above the medial malleolus. The Seldinger technique was then utilised to first pass a guide wire, followed by a 5 French EVLA sheath (Angiodynamics, Cambridge, UK). The tip of the sheath was sited at the SFJ under ultrasound guidance, venous blood aspirated to ensure position, and then flushed with normal saline.

The patient was tilted into the Trendelenburg position and perivenous tumescent anaesthesia administered via a spinal needle using a pedal-operated peristaltic pump (Nouvag DP-20, Nouvag, Goldach, Switzerland) along the GSV with the use of ultrasound guidance, at a target of 10ml tumescent per cm length of GSV. The solution comprised 20ml of 2% Lidocaine with 1:200,000 epinephrine (Xylocaine, AstraZeneca UK Ltd, Luton, UK) and 20 ml of 0.5% Levobupivacaine (Chirocaine, Abbott Laboratories Ltd, Maidenhead, UK) in 1000ml 0.9% Sodium Chloride for intravenous infusion (Baxter Healthcare, Newbury, UK).

Following tumescent infiltration, a 600μm bare-tipped laser fibre (AngioDynamics, Cambridge, UK) was introduced so that the tip of the laser fibre lay at the tip of the pre-positioned sheath. The sheath was then withdrawn by 3cm to expose the tip of the laser fibre; the sheath and laser fibre were locked together. An 810nm diode laser (AngioDynamics, Cambridge, UK) was fired, delivering a 14W continuous beam. The catheter and fibre were withdrawn at a predetermined rate calculated to deliver a specific LEED. Again, practices evolved during the course of the trial; the initial aim was to deliver 60-80 Jcm-1, but 100-120 $Jcm^{-1}$ became the target by the end of the study. Ambulatory phlebectomy of the premarked varicosities was performed through

2mm stab incisions, following infiltration of tumescent anaesthesia. Incompetent perforators that communicated directly with the GSV were not separately addressed. All phlebectomy sites were dressed with steri-strips, cotton wool and gauze and an elasticated self-adhesive compression bandage applied from foot to groin. Patients with C6 disease (active venous ulceration) were put into four-layer compression bandaging.

The primary outcome measure was QoL assessed by the SF36 generic instrument. Secondary outcome measures were: -

- QoL assessed by generic EQ5D and disease-specific AVVQ tools
- Clinical severity assessed by VCSS and CEAP
- Post-procedure pain scores and analgesia requirements
- Time to return to normal activity and work
- Patient satisfaction with i) cosmesis and ii) overall outcome

### 2.1.3: Follow-up protocol

At 2-year follow-up, all participants were asked to independently complete the same generic (SF36 and EQ5D) and disease-specific (AVVQ) QoL tools, prior to any meeting with a member of the investigating team, to remove the potential for investigator influence.

Following this, participants were interviewed face-to-face by an experienced investigator. All participants were asked to score their satisfaction for i) overall outcome and ii) cosmesis, using a 10cm unmarked visual analogue scale (VAS) from 0 (completely unsatisfied) to 10 (completely satisfied).

Clinical examination was then undertaken, documenting CEAP Clinical classification and VCSS scores, and looking for evidence of clinical recurrence; defined as new varicose veins >3mm in diameter, not evident prior to 12 weeks following the index procedure. The trial database (Microsoft® Access; Microsoft, Redmond, Washington, USA) was also interrogated to identify participants who had developed recurrence earlier, but who had undergone additional treatment such that there were no varicosities evident at two-years. These participants were also included in the analyses,

on an intention-to-treat basis; patients with residual varicosities were carefully excluded, as previously described[378].

A full venous DUS examination was subsequently undertaken in all patients by an experienced investigator with formal accreditation in vascular ultrasound.

## 2.1.4 DUS protocol

All DUS examinations were performed using the same high-quality ultrasound machine (Toshiba Aplio MX [Toshiba Medical Systems Ltd, Crawley, UK] with a 4-12MHz linear array transducer, following a standardised protocol based on international consensus documents[146,180,181,185,332].

B-Mode settings, including focal zone, overall gain and time gain compensation were adjusted dynamically to maintain an optimal image. Tissue harmonic imaging and compounding were used to maximize image quality and accuracy of measurements. Doppler flow settings were typically set at 5-10cms$^{-1}$, with optimization of colour gain and filters and an angle of insonation of 45° to the longitudinal vessel axis.

Patients were assessed whilst standing in a warm room with dimmed ambient lighting, initially facing the examiner, with the subject leg slightly flexed at the knee and externally rotated to expose the groin. The patient's weight was transferred onto the contralateral leg. The study commenced with identification of the SFJ in transverse section. Assessment for incompetence was performed using manual flow augmentation at a site greater than 10 cm distal to the region of insonation (or the foot when interrogating the distal calf), with sudden release. Incompetence was defined as retrograde flow greater than or equal to 1 second and 0.5 second on spectral Doppler for the deep and superficial veins respectively. The groin was then assessed for possible sources of reflux including the SFJ, abdominal or pelvic veins, groin tributaries, accessory veins, perforators and neovascularisation. During detailed anatomical and haemodynamic mapping, the entire GSV and its tributaries were assessed from groin to ankle, followed by any other incompetent veins emanating from the groin, thigh or calf. Anteroposterior measurements of vessels were made at predetermined locations using the ultrasound system's electronic calipers positioned at the most anterior echo of the anterior wall and the most posterior echo of the posterior wall of the vein. These were measured to the nearest 0.1 mm. These predetermined

locations along the GSV were 2cm from the SFJ, proximal thigh (10cm from the SFJ), knee level, and distal ankle level (2cm superior to the medial malleolus).  The patency of the superficial system was assessed using colour duplex and compression.

The deep system was then assessed from the groin to the knee; continuous flow, pulsatile flow, obstruction, thrombosis, or incompetence involving the CFV were indications to extend the examination to include the iliac veins and IVC and lead to consideration of other modalities of imaging (as did the presence of incompetence in the groin emanating from abdominal or pelvic tributaries), where there was any doubt over anatomical or haemodynamic status.

The patient was then repositioned to face away from the examiner and their hip was returned to the anatomical position for assessment of the SPJ, SSV and the deep veins of the calf. Initially the SSV was identified at the ankle and then assessed and traced proximally back to the SPJ. The position of the junction was noted and the examination went on to assess the other proximal and distal tributaries including the Giacomini vein, which, where present, was followed to its termination. Again a search was made for any incompetent perforators, before finally the popliteal and crural veins were assessed for patency and reflux.

## 2.1.5 Outcome Reporting

Outcomes from the 2-year follow-up visit were divided into three categories: clinical, QoL and DUS outcomes.

### Clinical Outcomes

- Presence of clinical recurrence of varicosities, irrespective of symptomatology
- VCSS and CEAP to assess either improvement or worsening of clinical severity over time.
- Patient satisfaction with i) cosmesis and ii) overall outcome on 10cm VAS

### QoL Outcomes

- SF36
- EQ5D
- AVVQ

- Anatomical success, defined as successful ablation of the GSV, demonstrated by lack of flow or absence of the vessel of the entire treatment length.
- Presence of reflux and patterns of distribution of any insufficiency
- GSV shrinkage rates

Results were compared for intergroup differences (EVLA versus surgery), followed by an in-depth intragroup comparison and analysis of those with and without clinical and/or DUS recurrence, with the aim of identifying factors that could improve patient outcomes.

## 2.2: Study 2: Buffering of Tumescent anaesthesia: finding the optimum solution

Commercially-available local anaesthetic preparations, commonly used in EVTA and routinely used in clinical practice at the Academic Vascular Surgical Unit, underwent serial pH-testing.

The basic solutions under test were: -
- 1 % Lidocaine (B. Braun Medical Ltd, Sheffield, UK)
- 1% Lidocaine with 1:200 000 Epinephrine (Xylocaine, AstraZeneca UK Ltd, Luton, UK)
- 2% Lidocaine with 1:200 000 Epinephrine (Xylocaine, AstraZeneca UK Ltd, Luton, UK)

Testing was performed using an Oakton/Eutech instruments pH 11 meter (Oakton Instruments, Vernon Hills, Illinois, USA), after two-point calibration with buffers at pH 4.01 and pH 7.00. Analyses were undertaken in the biochemistry laboratory at Hull Royal Infirmary, which was air-conditioned and temperature-controlled at a constant 21°C; the Surgical Outpatient Theatre, where EVLA is performed, is also temperature-controlled to 21°C. Three measurement runs were undertaken on three separate occasions, to account for subtle variations in ambient temperature and any

slight inaccuracies in preparation of the solutions. This gave a total of nine pH readings for each solution. Between each test, the pH probe was rinsed thoroughly in distilled water. The solution was slowly stirred with the fully-immersed probe, in order to ensure a homogenous solution. The pH meter was given sufficient time for the reading to stabilize.

The standard solution used in current clinical practice is as follows:-

Standard Tumescent Anaesthetic Solution

- 1000ml bag of 0.9% Sodium Chloride for intravenous infusion (Baxter Healthcare, Newbury, Berkshire, UK), 100ml extracted to leave 900ml, to which 100ml 1% Lidocaine with 1:200,000 Epinephrine (Xylocaine, AstraZeneca UK Ltd, Luton, UK) was added.

This therefore gives a solution of 0.1% Lidocaine with 1:2000,000 Epinephrine. This was pH tested, then subsequently titrated to physiological pH by buffering with 2ml incremental quantities of 8.4% Sodium Bicarbonate (Martindale Pharmaceuticals Ltd, Wooburn Green, UK). Again, three measurement runs were undertaken on three separate occasions.

Mean (SD) values are reported, along with hypothesis testing to confirm that the pH figures obtained for each solution were significantly different.

## 2.3: Study 3: Cohort study of Buffered versus Unbuffered tumescent anaesthesia

The optimal solution in terms of pH from Study 2 was selected and taken forward for clinical testing during routine EVLA plus AP. A cohort of consecutive patients undergoing routine EVLA for primary, symptomatic, GSV insufficiency was chosen.

EVLA was performed on a day-case, outpatient basis as per the standard practice in the Academic Vascular Surgical Unit, (detailed below) in the Surgical Outpatient Theatre at Hull Royal Infirmary. For each participant, the investigating team confirmed consent to undergo the procedure and take part in follow-up review. Prior to treatment, patients were asked to complete a questionnaire containing SF36, EQ5D

and AVVQ QoL tools. CEAP clinical classification and VCSS scores were also documented for each patient, in addition to standard demographic details and DUS characteristics.

### EVLA procedure

Patients deemed to be at high risk of venous thromboembolism, using the standardised trust pre-operative risk-assessment proforma, received a single pre-operative dose of prophylactic low molecular weight heparin (LMWH), as per standard NHS practice.

Patients underwent pre-operative DUS-guided marking by the operating surgeon to identify the Saphenofemoral Junction (SFJ), the lowest point of reflux of the GSV, any incompetent perforating veins and varicose tributaries. The patient was then positioned on the operating table and underwent sterilization of the leg to be treated using 7.5% Povidone-Iodine (Videne®, Ecolab Ltd, Leeds, UK); patients with an iodine allergy received 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK). Sterile draping was subsequently performed in the standard fashion.

With the patient in the reverse Trendelenburg position to enhance venous filling, the GSV was cannulated using a 0.035" access kit at the lowest point of demonstrable reflux under local anaesthesia with ultrasound guidance. Local anaesthesia to skin was 1% Lidocaine with 1:200,000 epinephrine, buffered with 8.4% sodium bicarbonate in a 10:1 ratio as per the Cochrane review[394]. The Seldinger technique was then utilised to first pass a guide wire, followed by the EVLA sheath. Small-calibre veins were accessed with the additional assistance of a 0.018" 'micro-access' kit. Tortuous GSVs that would not permit passage of the standard 0.035" guidewire were navigated with the use of a hydrophilic guidewire (HiWire®, Cook Medical, Hitchin, UK). The tip of the sheath was sited at the SFJ under ultrasound guidance, venous blood aspirated to ensure position, and then flushed with normal saline.

The tumescent solution was made as per the standard, currently utilised solution (see Standard Tumescent Anaesthetic Solution, p.118), i.e 0.9% NaCl with 0.1% Lidocaine and1:2000,000 Epinephrine, unbuffered.

The solution was buffered to pH 7.4 with the addition of 10ml 8.4% Sodium

Bicarbonate (Martindale Pharmaceuticals Ltd, Wooburn Green, UK), as outlined in Study 2.

This tumescent solution is widely used in a number of applications in routine surgical and dermatological procedures, including ClosureFAST RFA (Venefit procedure).

The patient was tilted into the Trendelenburg position and perivenous tumescent anaesthesia administered via a spinal needle using a pedal-operated peristaltic pump (Nouvag DP-20, Nouvag, Goldach, Switzerland) along the GSV with the use of ultrasound guidance, at a target of 10ml tumescent per cm length of GSV.

Following tumescent infiltration, a 600μm jacket-tipped laser fibre (NeverTouch, AngioDynamics, Cambridge, UK) was introduced so that the tip of the laser fibre lay at the tip of the pre-positioned sheath. The sheath was then withdrawn by 3cm to expose the tip of the laser fibre, thus leaving the fibre tip at the SFJ, aiming for a flush occlusion; the sheath and laser fibre were then locked together. An 810nm laser (AngioDynamics, Cambridge, UK) was fired, delivering a 14W continuous beam. The catheter and fibre were withdrawn at a rate of 2mm/sec, delivering a target LEED of 100Jcm$^{-1}$. The specific energy delivered and length of vein treated was recorded for each patient.

Ambulatory phlebectomy of the premarked varicosities was performed through 2mm stab incisions, following infiltration of tumescent anaesthesia. Incompetent perforators that communicated directly with the GSV were not separately addressed. All phlebectomy sites were dressed with Steri-Strips™ (3M UK PLC, Bracknell, UK), cotton wool and gauze and an elasticated self-adhesive compression bandage applied from foot to groin. Patients with C6 disease (active venous ulceration) were put into four-layer compression bandaging.

Immediately following the procedure, patients were asked to score the periprocedural pain they experienced on a 10cm unmarked VAS from 0, "No pain" to 10 "Worst imaginable pain".

Patients were encouraged to mobilise immediately and were discharged home with oral paracetamol and diclofenac to be used as required. A one-week VAS pain and

analgesia usage diary was given to each patient; they were advised to complete the pain score at the end of each day.

Follow-up visits (at the Vascular Laboratory, Academic Vascular Surgical Unit, Hull Royal Infirmary) were scheduled for one, six and twelve weeks. At each visit, patients were asked to independently complete the same QoL tools (detailed below), prior to meeting with an investigator.

At the first visit, the bandaging was removed and exchanged for a full-length graduated compression stocking, (T.E.D.™, Tyco Healthcare, Gosport, UK), giving 18mmHg compression at the ankle, after clinical and DUS assessment (as described in Study 1), to be worn during the day for a further 5 weeks until the next follow-up visit. Each visit covered:-

- Clinical assessment: -

  - Adverse events/reactions/complications in accordance with the Society of Interventional Radiology Standards of Practice Committee Guidelines on reporting complications[414]

  - Residual / recurrent varicosities

  - CEAP classification

  - VCSS

  - Patient satisfaction rating scales

- DUS examination

  - Assessment of Deep and Superficial venous systems, particularly looking for DVT and successful occlusion of the GSV

Outcomes for the cohort of patients receiving buffered tumescent anaesthesia were compared to a historical cohort of patients, identified from a prospectively maintained venous database, who had undergone the identical EVLA procedure with the standard (unbuffered) tumescent solution. The primary outcome measure was periprocedural pain.

Secondary outcome measures were: -

- Post-procedure pain scores
- Complications
- Time to return to normal activity and work

- Clinical severity assessed by VCSS
- Patient satisfaction with i) cosmesis and ii) overall treatment
- QoL assessed by generic (SF36 and EQ5D) and disease-specific (AVVQ) tools
- Additional analyses of DUS outcomes were undertaken to identify any aspects of the current EVLA technique that could be further optimized.

# 2.4: Study 4: Prospective cohort study of concomitant phlebectomy or sclerotherapy of varicosities

Consecutive patients undergoing EVLA with AP for GSV varicose veins were compared with a subsequent cohort of consecutive patients who received the same EVLA procedure, but underwent UGFS of their varicosities with 1% Sodium Tetradecylsulphate (Fibrovein™, STD Pharmaceutical products Ltd, Hereford, UK).

The EVLA procedure was performed as described in Study 3, with standard unbuffered tumescent anaesthesia. Patients then underwent AP (as also described earlier), or UGFS of the visible varicosities.

### UGFS procedure

Prior to infiltration of tumescent anaesthesia in the EVLA procedure, the varicosities were cannulated under ultrasound guidance with either a 20 or 22 gauge intravenous cannula (Vasofix® Safety, B. Braun Medical Ltd, Sheffield, UK), venous blood aspirated to confirm position and flushed with 0.9% NaCl.

After conclusion of the EVLA procedure, up to 12ml of foam was produced using the Tessari technique[324] with room air and 1% Sodium Tetradecylsulphate (Fibrovein™, STD Pharmaceutical products Ltd, Hereford, UK) in a 3:1 ratio, with at least 20 passes between two 12ml syringes and a 3-way tap (B. Braun Medical Ltd, Sheffield, UK). This foam was injected and "milked" into all visible varicosities within a maximum of 60 seconds from production. Dressings and bandaging was then administered as described in Study 3.

Patients were encouraged to mobilise immediately and were discharged home with oral paracetamol and diclofenac to be used as required. A one-week VAS pain and analgesia usage diary was given to each patient; they were advised to complete the pain score at the end of each day.

Follow-up visits (at the Vascular Laboratory, Academic Vascular Surgical Unit, Hull Royal Infirmary) were scheduled for one, six and twelve weeks. At each visit, patients were asked to independently complete the same QoL tools as detailed previously, prior to meeting with an investigator.

At the first visit, the bandaging was removed and exchanged for a full-length graduated compression stocking, after clinical and DUS assessment (as described in Study 1), to be worn during the day for a further 5 weeks until the next visit.

Patients were reviewed at one, six and twelve weeks post-operatively. Outcome measures were: -

*Clinical Outcomes*

- Presence of any complications, as per Study 3
- Postprocedural pain scores
- VCSS to assess change of clinical severity over time.
- Patient satisfaction with i) cosmesis and ii) overall outcome on 10cm VAS
- Residual varicosities
- Requirement for additional procedures

*QoL Outcomes*

- SF36
- EQ5D
- AVVQ

*DUS outcomes*

- Anatomical success, defined as successful ablation of the GSV, demonstrated by lack of flow or absence of the vessel of the entire treatment length.
- Absence / presence of DVT

The primary outcome measure was freedom from residual varicosities at 12 weeks. As in Study 3, additional analyses of DUS outcomes were undertaken to identify any aspects of the current EVLA technique that could be further optimized.

## 2.5: Study 5: Prospective cohort study of 810nm versus 1470nm EVLA

A prospective cohort study of 2 consecutive patients groups undergoing EVLA for primary, symptomatic GSV reflux was undertaken. The first group of patients underwent EVLA with an 810nm diode, 14Watt continuous power delivery, at a target LEED of 80-100 $Jcm^{-1}$, as per study 3, under standard unbuffered tumescent anaesthesia. The second group of patients underwent EVLA following the same processes, but with a 1470nm diode laser, 8Watt continuous power at a target of 40-60 $Jcm^{-1}$ as per the manufacturers recommendations. The NeverTouch jacketed laser fibre was used in all patients. The specific energy delivered and length of vein treated was recorded for each patient.

Patients were encouraged to mobilise immediately and were discharged home with oral paracetamol and diclofenac to be used as required. A one-week VAS pain and analgesia usage diary was given to each patient; they were advised to complete the pain score at the end of each day.

Follow-up visits (at the Vascular Laboratory, Academic Vascular Surgical Unit, Hull Royal Infirmary) were scheduled for one, six and twelve weeks. At each visit, patients were asked to independently complete the same QoL tools, prior to meeting with an investigator.

At the first visit, the bandaging was removed and exchanged for a full-length graduated compression stocking, after clinical and DUS assessment (as described in Study 1), to be worn during the day for a further 5 weeks until the next visit.

Patients were reviewed at one, six and twelve weeks post-operatively. Outcome measures were: -

*Clinical Outcomes*

- Presence of any complications
- Postprocedural pain scores and analgesia requirements
- VCSS and CEAP to assess change of clinical severity over time.
- Patient satisfaction with i) cosmesis and ii) overall outcome on 10cm VAS
- Residual varicosities
- Requirement for additional procedures

*QoL Outcomes*

- SF36
- EQ5D
- AVVQ

*DUS outcomes*

- Anatomical success, defined as successful ablation of the GSV, demonstrated by lack of flow or absence of the vessel of the entire treatment length.
- Absence / presence of DVT

The primary outcome measure was post-procedural pain over the first seven days. Additional analyses of DUS outcomes were undertaken to identify any aspects of the current EVLA technique that could be further optimized, as in the preceding studies.

# 2.6: Data handling and statistical analysis

All outcomes were documented and reported as per international consensus[146,332] in a dedicated venous database (Microsoft® Access; Microsoft, Redmond, Washington, USA). All data analyses were undertaken using IBM® SPSS® Statistics version 19.0.

## Continuous data

The distribution of continuous data was explored using histogram analysis, evaluating for normality, with assessment of skewness and kurtosis. The Shapiro-Wilk (SW) and Kolmogorov-Smirnov (K-S) statistical tests were used to establish the certainty over any assumption of normality; significance values greater than 0.050 were assumed to indicate normal distribution.

Normally distributed (parametric) data are quoted as mean (95% confidence interval, CI) for dependent variables or mean (standard deviation, SD) for independent variables. Non-parametric data are quoted as median (inter-quartile range, IQR).

Intragroup comparisons featured the analysis of paired data (i.e. different time-points in the same patient) and intergroup comparisons (i.e. from different study arms) used unpaired data. Hypothesis testing was performed comparing groups according to the data distribution and whether paired or unpaired. Quoted p-values represent the probability of having observed the data if the null hypothesis ($H_0$) were true. p-values are quoted to three decimal places and values of $p < 0.050$ were regarded as significant and led to rejection of the null hypothesis. These statistically significant differences were then examined to establish whether they represented clinically significant findings in the context of this research and the existing evidence base.

The following hypothesis tests were used according to the nature of the data under interrogation:

*Parametric data:*

- **Paired**
    - paired Student t-test (2 samples)
    - ANOVA (multiple related samples)

- **Unpaired**
    - unpaired Student t-test

*Non-parametric data:*

- **Paired**
    - Wilcoxon signed rank test (WSR test) (2 samples)
    - Friedman ANOVA (F-A) (multiple related samples)

- **Unpaired**
    - Mann-Whitney U test (MWU test)

## Categorical data

Simple categorical data is presented as percentages (x/y) where x represents the number of cases in a category and y represents the total number of cases under consideration. When required, relative risk (RR), risk differences (RD) and number needed to treat (NNT) is also quoted along with 95 confidence intervals.

The primary hypothesis test used in categorical analysis was Pearson's Chi-square test ($\chi^2$ test). If greater than 20% of expected frequencies were less than 5 or any were below 1, then Fisher's exact test (FET) was used.

Freedom from clinical recurrence in Study 1 was calculated using Kaplan-Meier analysis, featuring intergroup Log Rank significance testing, as recommended by international consensus[146].

Logistic regression was used in Study 1 to isolate the effect of various DUS patterns of reflux on development of clinical recurrence, correcting for the effect of key confounding variables (age, sex, BMI, LEED and the length of vein treated). Standard testing of the key assumptions of these models was performed. The forced entry method was used.

Receiver Operator Characteristic (ROC) analyses with Area Under the Curve (AUC) values were calculated for the ability of periprocedural pain to predict the use of buffered tumescent anaesthesia in Study 3, and for wavelength to determine the degree of postprocedural pain in Study 5.

## 2.7: Ethics

### Research Governance

All studies were conducted in accordance with principles laid down in the declaration of Helsinki, International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines; and the Research Governance Framework for Health and Social Care. All investigators associated with the research programme have undertaken Good Clinical Practice (GCP) training.

In the context of this research programme, patients were only offered intervention if both patient and surgeon felt that on balance this would result in a significant benefit to that individual, after a full discussion of potential risks, complications and benefits. Inclusion into the HELP-1 RCT was only entertained if both parties occupied a position of equipoise over the optimal procedure to be undertaken. All patients were made aware of the additional burden of the assessments associated with the research and were aware that they could withdraw at any stage of the research process, without any cost or prejudice to their existing, on-going or future care. The use of one-stop venous clinics minimized the burden of follow-up to patients; indeed it was seen as a benefit of taking part to many.

The central aim of this research programme was to optimise patient care and outcomes by providing reliable information of the known efficacy, benefits and risks of the newer techniques in the management of SVI when compared to the gold standard treatment of conventional surgery. These principles echoed the current position on EVLA by NICE, which "…support[s] the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance…"[415]. In its advice to patients undergoing EVLA, NICE recommend that "…the patient understands what is involved and agrees (consents) to the treatment, and… the results of the procedure are monitored." "NICE has also encouraged doctors who perform endovenous laser treatment to collect information about how well it works in patients over a longer period of time."[416]. These statements further vindicate the aims and objectives of this thesis.

The protocols upon which this thesis is based were prospectively designed based on current evidence, with the relevant approvals sought and secured from both Research Ethics Committees (REC) and the institutional review board (Hull and East Yorkshire Hospitals NHS Trust Research and Development Department, "HEY R&D").

## Data Handling and Record Keeping

The Principal Investigator is responsible for data collection, recording and quality. Electronic data are stored on a Trust computer within the Vascular Laboratory at Hull Royal Infirmary. Hull and East Yorkshire Hospitals NHS Trust IT Services Department has a backup procedure approved by auditors for disaster recovery. Servers are backed up to tape media each night; the tapes run on a 4-week cycle. Files stay on the server unless deleted by accident or deliberately. Anything deleted more than 4 weeks previously is therefore lost. Additional 'archive' backups are taken for archived data, so data should not be lost from this type of system e.g. FileVision which stores Medical Records. Tapes are stored in a fireproof safe. Study documents (paper and electronic) will be retained in a secure location and kept locked when not in use during and after the studies have finished. All essential documents including source documents will be retained for a minimum period of 5 years after study completion (last visit of last patient). A label stating the date after which the documents can be destroyed is be placed on the inside front cover of the casenotes of trial participants. Data were collected and retained in accordance with the Data Protection Act 1998.

## Access to Source Data

The investigators and institution will permit monitoring, audits, REC and MHRA review where applicable and provide direct access to source data and documents.

## Finance

The studies reported in this thesis are funded through the Academic Vascular Surgical Unit at Hull Royal Infirmary. Participants did not receive any financial incentive to take part in any study. Diomed/Angiodynamics (Cambridge, UK) also provided 50% of a research nurse's salary over the first 12 months of the HELP-1 RCT, but had no involvement or influence in the design, subsequent data collection, analysis, writing-up, or decisions to submit for publication. Diomed have no access to any unpublished data. Full responsibility for the integrity of the data, accuracy of analyses and their

interpretation is taken by the research team. There are no conflicts of interest from any individual associated with this research programme.

## Indemnity

These are NHS-sponsored research studies. Any negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by HEY R&D. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. The University of Hull has an insurance policy that includes cover for no-fault compensation in respect of accidental injury to a research subject.

# Chapter 3: Results

## 3.1 Study 1: Two-year clinical, QoL and DUS outcomes from the HELP-1 RCT

Of the 137 and 139 patients that received intervention, 111 (79%) and 116 (83%) patients in the Surgery and EVLA groups respectively attended two-year follow up as planned (Figure 3); there was no statistical difference in loss to follow-up between the groups (p=0.597, $\chi^2$).
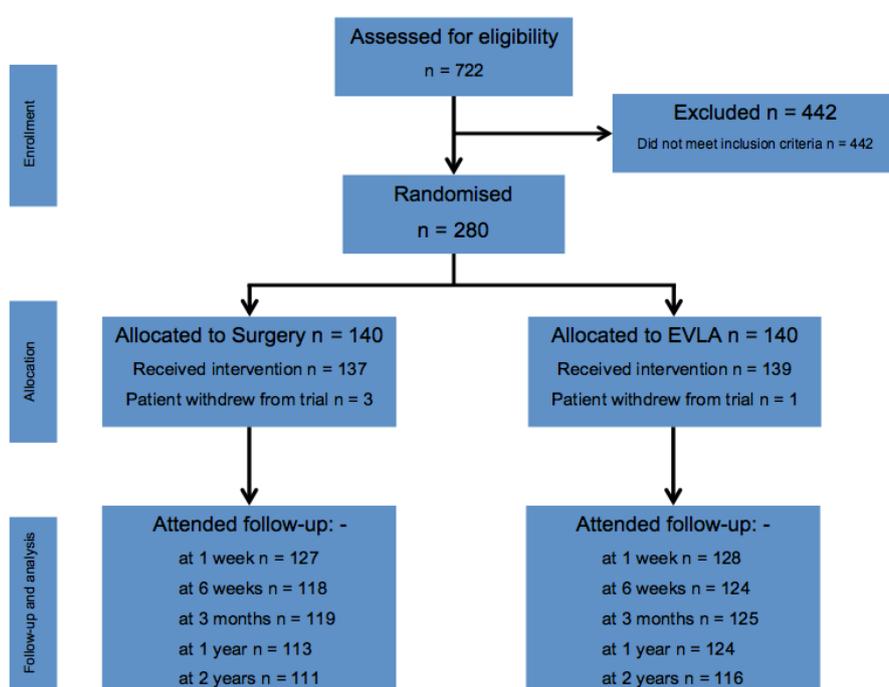


**Figure 3: CONSORT diagram (Study 1)**

Of all the patients attending 2-year follow-up, only one patient had failed to attend at 1-year follow-up; they were found to have clinical recurrence at 2 years. Patients who failed to attend their first appointment were sent a second chance. Telephone contact was then attempted for those that still failed to attend. In those with whom telephone contact was successful (Surgery n = 14, EVLA n = 16), all reported being happy with the outcome and either felt no reason or could not spare the time to attend further follow-up. These patients were informed that they would be invited to attend follow-up again at 5 years from treatment, in keeping with the study protocol. None of the patients that failed to attend two-year follow-up had been identified as having clinical or DUS recurrence at their last contact.

## Clinical Outcomes

### Clinical Recurrence

Evidence of clinical recurrence at up to 2 years was significantly more likely in the surgery group: 30 (27%) of 111 versus 16 (13.8%) of 116 (p=0.013, $\chi^2$ test), meaning freedom from recurrence at 2 years was seen in 73% and 86.2% of surgery and EVLA patients, respectively, in those attending follow-up. Assuming that none of the patients lost to follow-up had clinical recurrence, freedom from recurrence at 2 years was 78.1% and 88.5%. Figure 4 shows a Kaplan-Meier survival plot of freedom from recurrence up to 2 years; patients lost to follow-up are excluded.
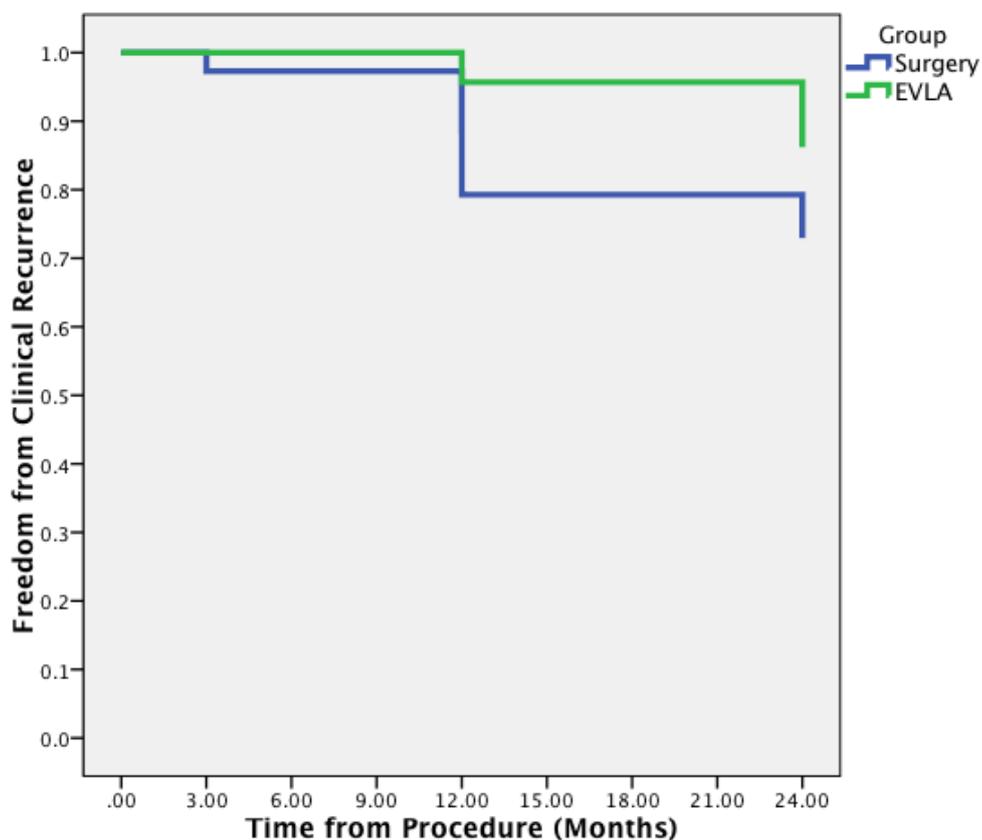


**Figure 4: Kaplan-Meier Survival plot for freedom from clinical recurrence (Study 1)**

p=0.013 at two years

### VCSS

The median (iqr) VCSS at 2 years was 0 (0-1) for patients in both groups (p=0.373, MWU). This maintained the improvements seen in the short term, with statistically significant improvements over time from pre-procedural values (p<0.001, Friedman's Test); there were no intragroup differences at any postoperative time point (Related-samples WSR Test), (Figure 5).

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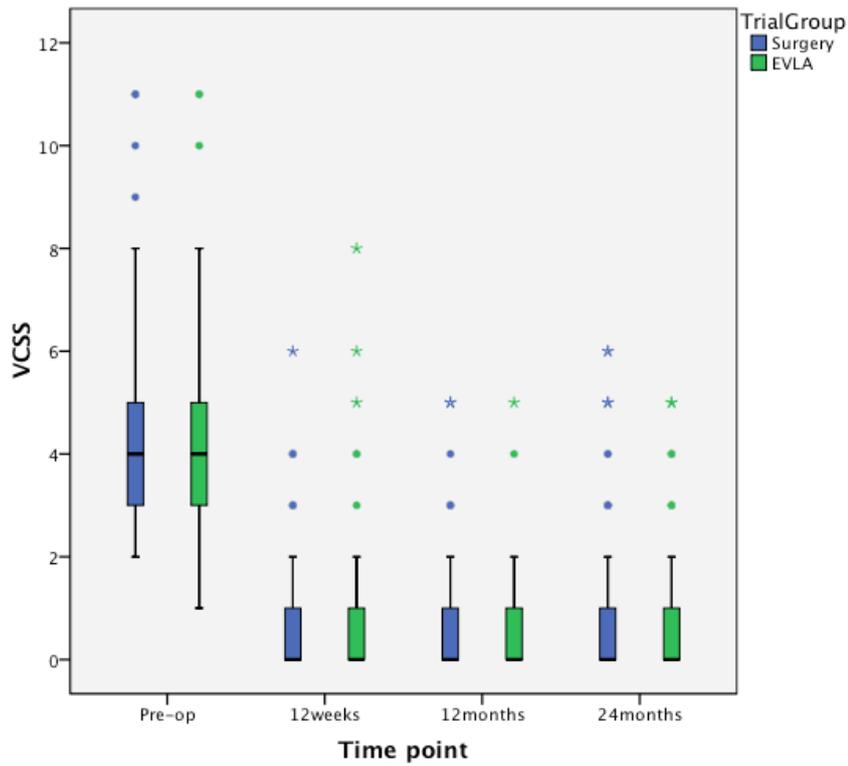
**Figure 5: VCSS over time by group (Study 1)**

However, looking at patients with evidence of clinical recurrence, VCSS scores were significantly higher (worse) than for patients with freedom from recurrence (p<0.001, MWU) (Figure 6).
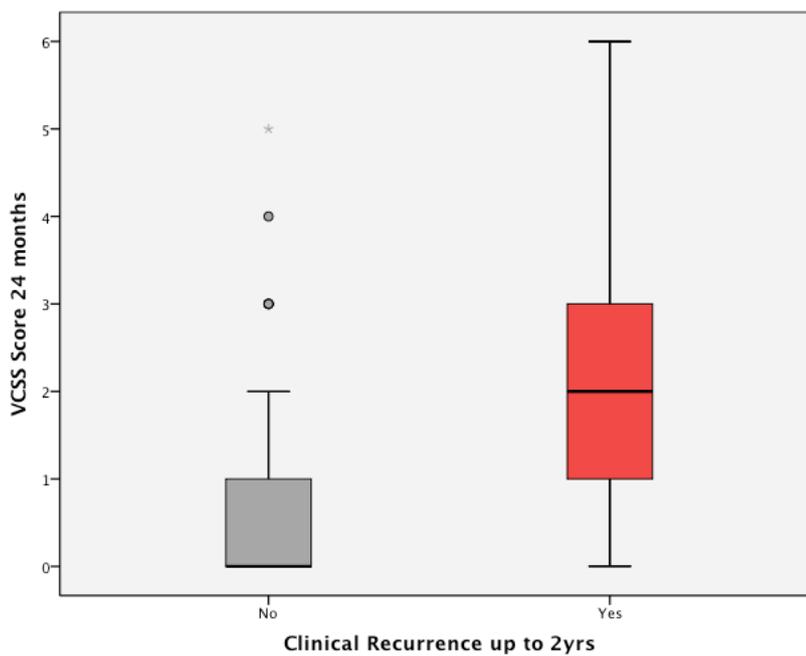


**Figure 6: VCSS over time - Recurrence versus No recurrence (Study 1)**

Whilst CEAP is an insensitive measure of clinical responsiveness, there were no statistically significant differences in clinical severity between surgery and EVLA at 2 years (p = 0.830, $\chi^2$) (Figure 7).
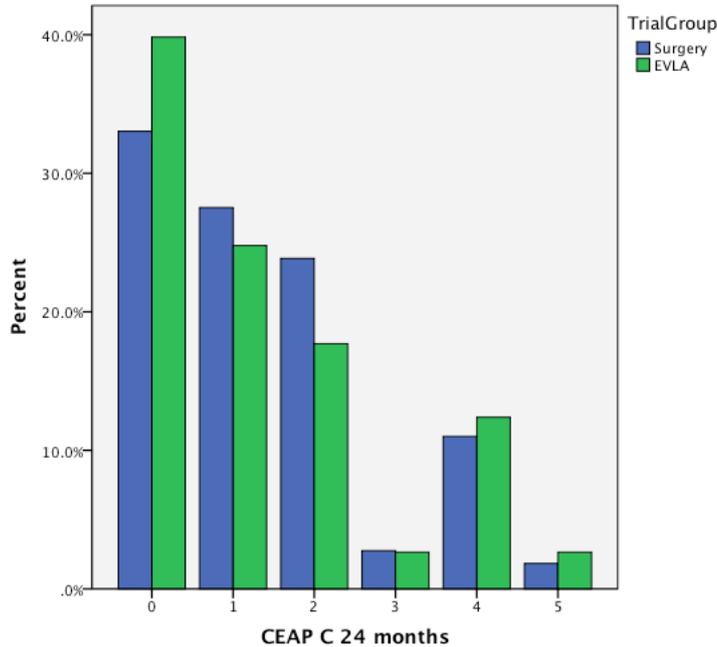


**Figure 7: CEAP Clinical Classification at 2 years (Study 1)**

*Patient Satisfaction*

| | Surgery (n= 111) | EVLA (n= 116) | p[*] |
|---|---|---|---|
| **Patient Satisfaction** | | | |
| with overall outcome | 10 (9-10) | 10 (9-10) | 0.218 |
| with cosmesis | 10 (8-10) | 9 (8-10) | 0.578 |

**Table 8: Patient satisfaction with Surgery and EVLA at 2 year follow-up.**

Values reported are median (iqr), [*]: MWU test

There were no differences between surgery and EVLA groups in the high patient-reported satisfaction scores at 2 years (Table 8). However, patients with recurrence did report significantly lower satisfaction with both the overall treatment outcome (p=0.002, MWU) and cosmesis (p<0.001, MWU) than those with freedom from recurrence (Figure 8).
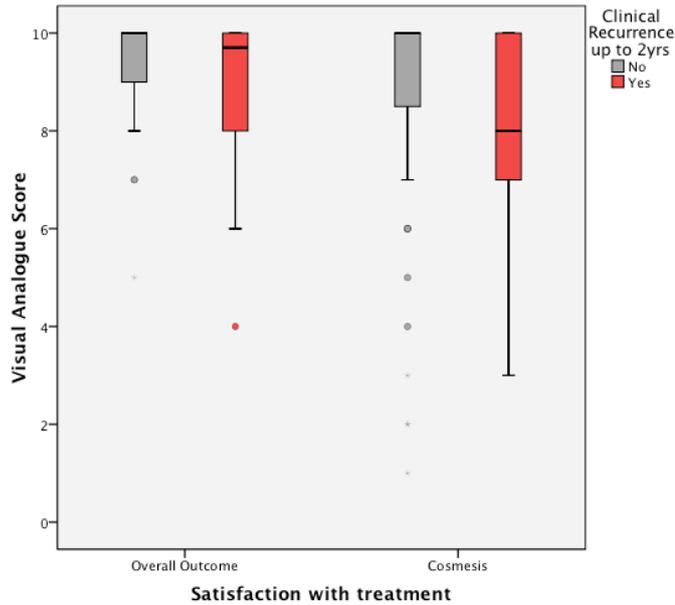
**Figure 8: Patient Satisfaction at 2 years: Clinical Recurrence versus No Recurrence (Study 1)**

## Quality of Life Outcomes

There were no intergroup differences between EVLA and Surgery in either the generic (SF36 & EQ5D) or disease specific (AVVQ) scores (Table 9) at 2 years.

| | Surgery (n= 111) | EVLA (n=116) | p[*] |
|---|---|---|---|
| **SF36** | | | |
| **Physical functioning** | 95 (85-100) | 90 (80-100) | 0.277 |
| **Role-physical** | 100 | 100 | 0.738 |
| **Bodily pain** | 84 (72-100) | 84 (62-100) | 0.814 |
| **General Health** | 77 (67-92) | 77 (62-92) | 0.396 |
| **Vitality** | 80 (60-85) | 70 (60-83.75) | 0.200 |
| **Social functioning** | 100 (75-100) | 100 (75-100) | 0.523 |
| **Role-emotional** | 100 | 100 | 0.757 |
| **Mental Health** | 84 (76-92) | 86 (68-100) | 0.608 |
| **EQ5D** | 1.00 (0.848-1.00) | 1.00 (0.845-1.00) | 0.119 |
| **AVVQ** | 2.52 (0-7.73) | 2.00 (0-7.32) | 0.321 |

**Table 9: QoL Outcomes at 2 years (Study 1)**

Values reported are median (iqr), [*]: MWU test

### *Intragroup Analysis: SF36 Domain Scores*

On intragroup testing (Related-samples WSR Test), there were no differences between the 1 and 2 year scores for any of the SF36 domain scores in the Surgery group (PF,

p=0.945; R-P, p=0.634; BP, p=0.328; GH, p=0.445; Vit, p=0.418; SF, p=0.248; R-E, p=0.468). While there were similarly no differences between 1 and 2 year scores for the SF36 domains of PF (p=0.074), R-P (p=0.175), SF (p=0.719) and R-E (p=0.792), the EVLA group did deteriorate over 1 year scores for BP (p=0.028), GH (p=0.001), Vit (p=0.038) and MH (p=0.023). However, the BP scores at 2 years remained significantly higher than baseline (p=0.001), with no differences between the same time-points for GH (p=0.667), Vit (p=0.246), or MH (p=0.607) (Figure S- 1, p.269).

*Intragroup Analysis: EQ5D Utility Index Scores*

Intragroup testing (Related samples WSR Test) revealed no differences between 1- and 2-year values for EQ5D in the Surgery (p=0.444) and EVLA (p=0.058) groups, with maintenance of improvement over baseline values for both groups (Surgery, p<0.001; EVLA, p<0.001) (Figure 9).
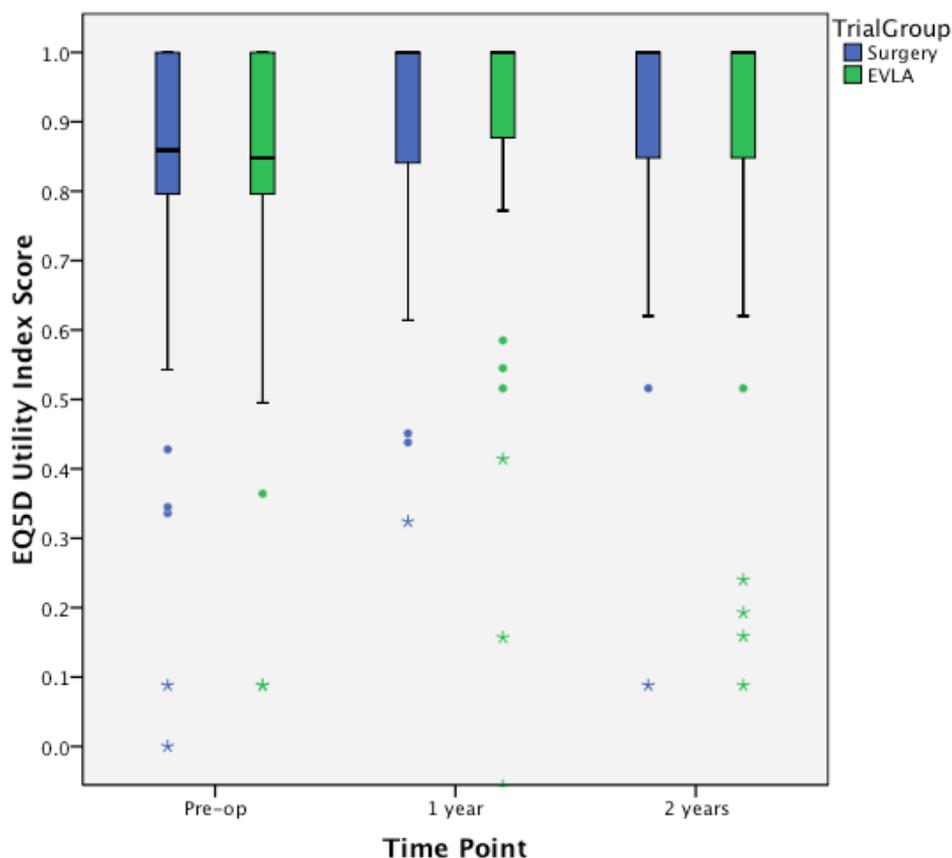


**Figure 9: EQ5D Utility Index Scores over time (Study 1)**

### Intragroup Analysis: AVVQ Scores

Intragroup testing (Related samples WSR) revealed no differences between 1- and 2-year values (median [iqr]) for AVVQ in either the Surgery (2 [0-5.74] versus 2.51 [0-7.32], p=0.058) or EVLA (2 [0-5.43] versus 2 [0-6.41], p=0.281) groups, with maintenance of improvement over baseline values for both groups (Surgery, p<0.001; EVLA, p<0.001) (Figure 10).
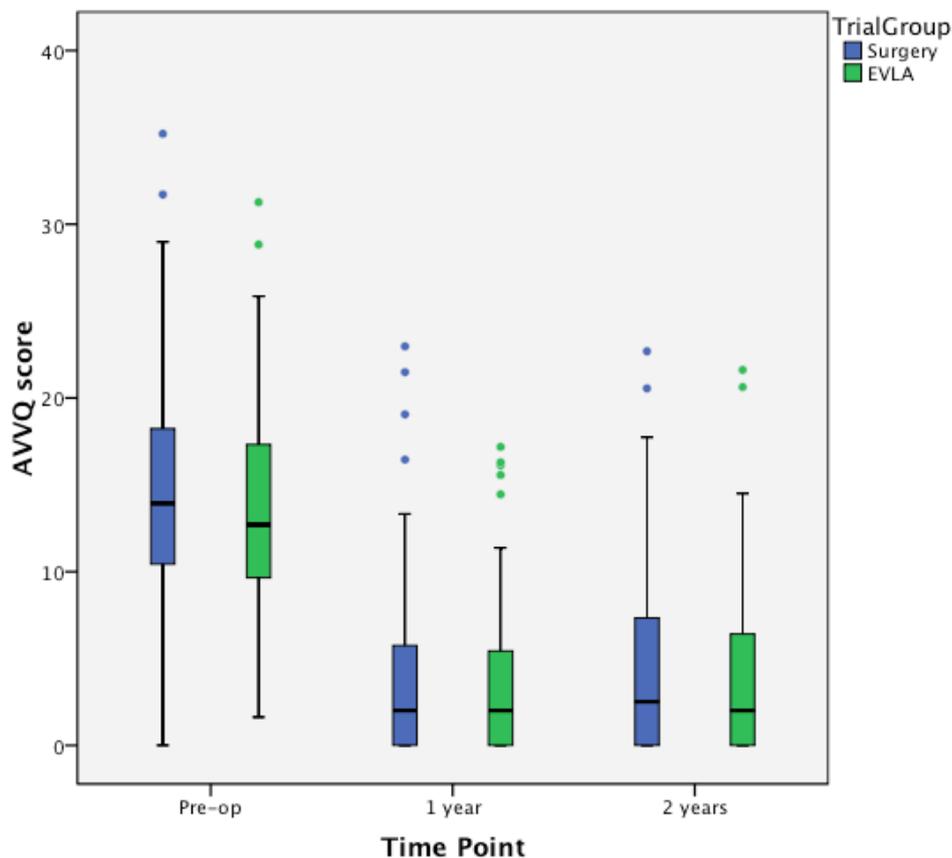


**Figure 10: AVVQ Scores over time (Study 1)**

### Clinical Recurrence versus Freedom from Recurrence

There were no differences in QoL scores for any SF36 domain (Figure S- 2, p.272) nor EQ5D utility index score (Figure S- 3, p.272) between patients with clinical recurrence compared to those with freedom from recurrence. However, patients with recurrence had significantly higher AVVQ scores (5.53 [2.34-10.50]) than those without recurrence (2.00 [0-5.51]), p<0.001 (Figure 11).

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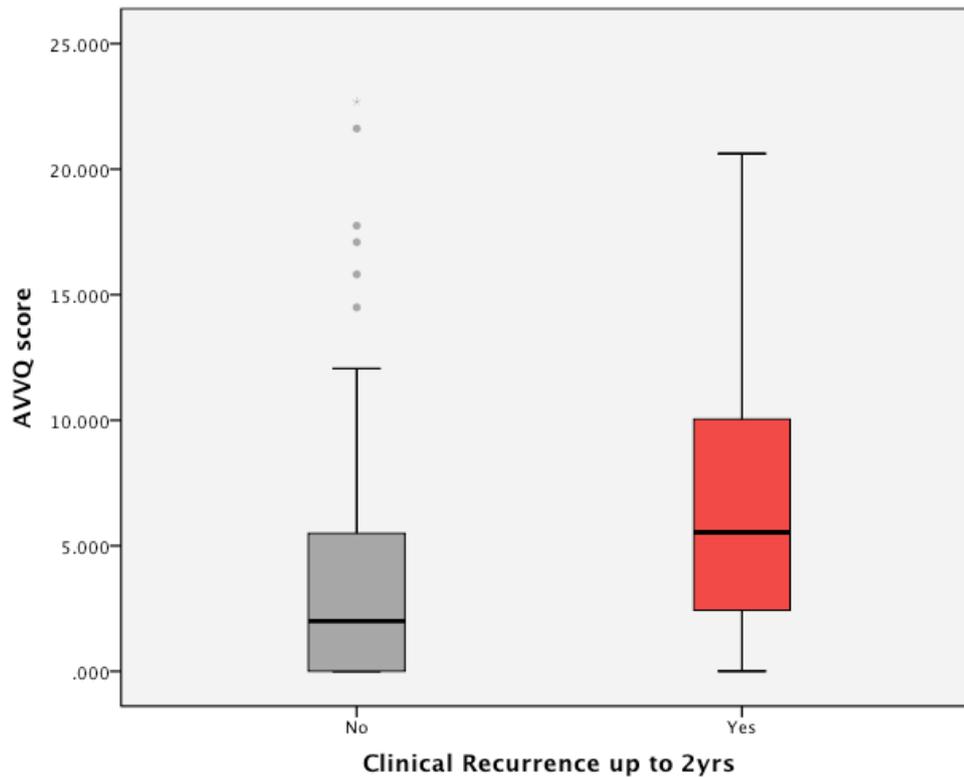
**Figure 11: AVVQ Scores at 2 years: Clinical Recurrence versus No Recurrence (Study 1)**

Patients with clinical recurrence at 2 years had significantly higher (worse) AVVQ scores than those with freedom from recurrence, p<0.001.

## Duplex Ultrasound Outcomes

There was no statistically significant difference in overall freedom from DUS-detected SFJ/GSV reflux in the treated length of vein between surgery (90.1%) and EVLA (94.2%) at 2 years (p=0.882). Complete absence/ablation of the treated GSV was identified in 90.9% and 92.1% in the Surgery and EVLA groups respectively (p=0.580), (Figure 12).
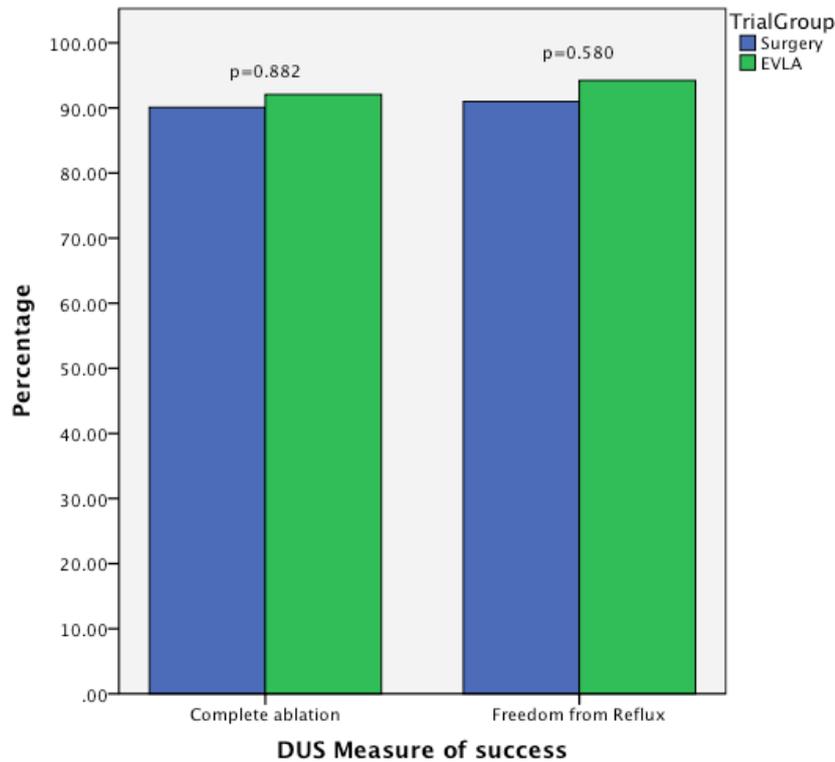
**Figure 12: DUS-determined treatment success at 2 years (Study 1)**

### Saphenofemoral Junction

Patients who underwent surgery were more likely to have a flush occlusion of the SFJ (94.4% versus 57.9%, p<0.001), although there were no differences in the relatively low rates of SFJ incompetence between Surgery (5.5%) and EVLA (11.4%), p=0.120. In keeping with these findings, patients who had undergone EVLA were more likely to demonstrate presence of proximal GSV tributaries, although there was no difference in the rates of reflux within these vessels between Surgery and EVLA. There was a 22% rate of neovascularization in the region of the previous SFJ in the surgery group, whereas this phenomenon was not seen in any cases following EVLA (p<0.001) (Figure 13).
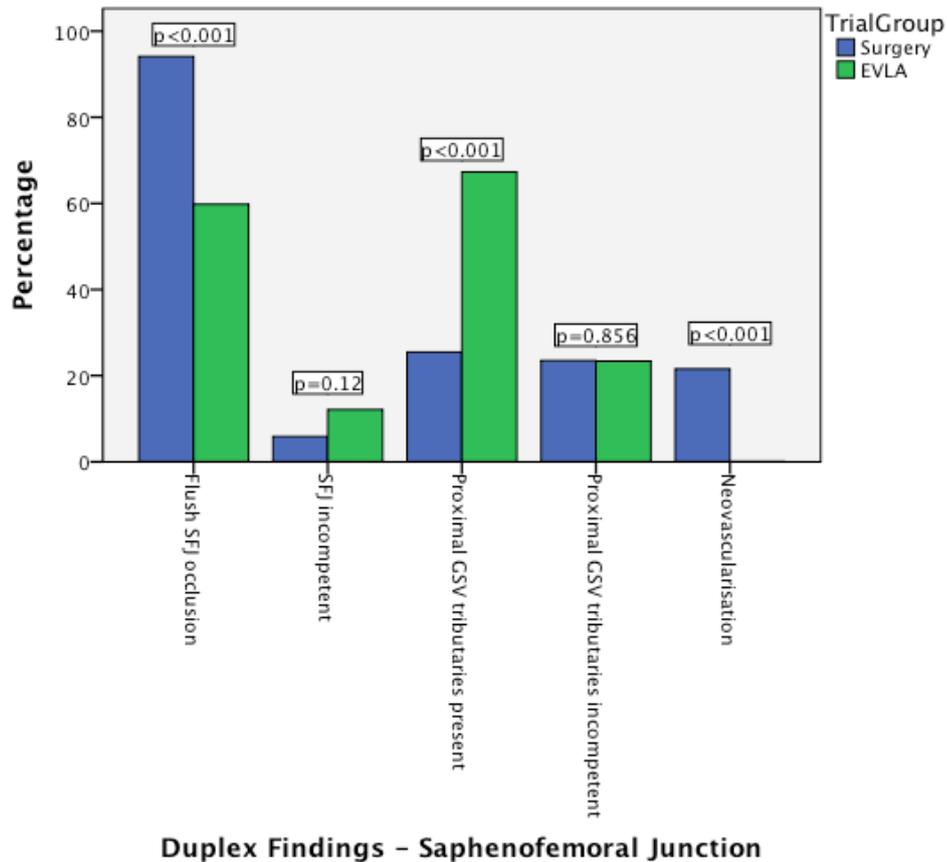
**Figure 13: DUS Characteristics of the SFJ at 2 years (Study 1)**

*GSV*

The presence of a DUS-detected proximal GSV was significantly less common in the Surgery group (4.6%) than EVLA group (61.4%), p<0.001, although there were no differences between the Surgery and EVLA groups in either presence of flow (4.6% versus 5.2%, p=0.828) or reflux (4.6% versus 4.4%, p=0.942) (Figure 14). These findings are mirrored in the mid- (Figure 15) and distal- (Figure 16) GSV.
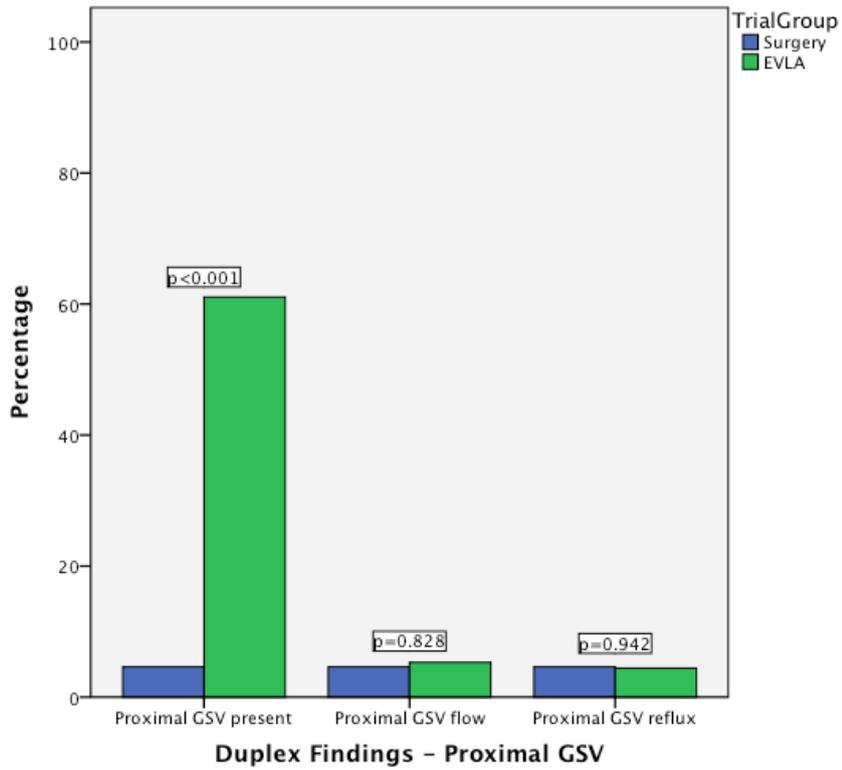
**Figure 14: DUS Characteristics of the Proximal GSV at 2 years (Study 1)**
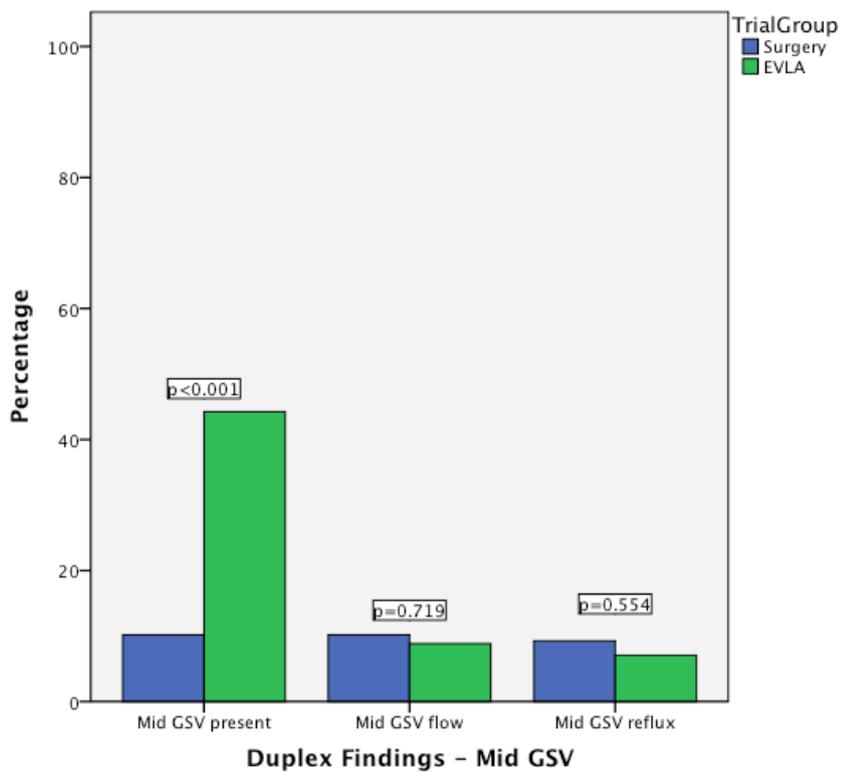


**Figure 15: DUS Characteristics of the Mid-GSV at 2 years (Study 1)**
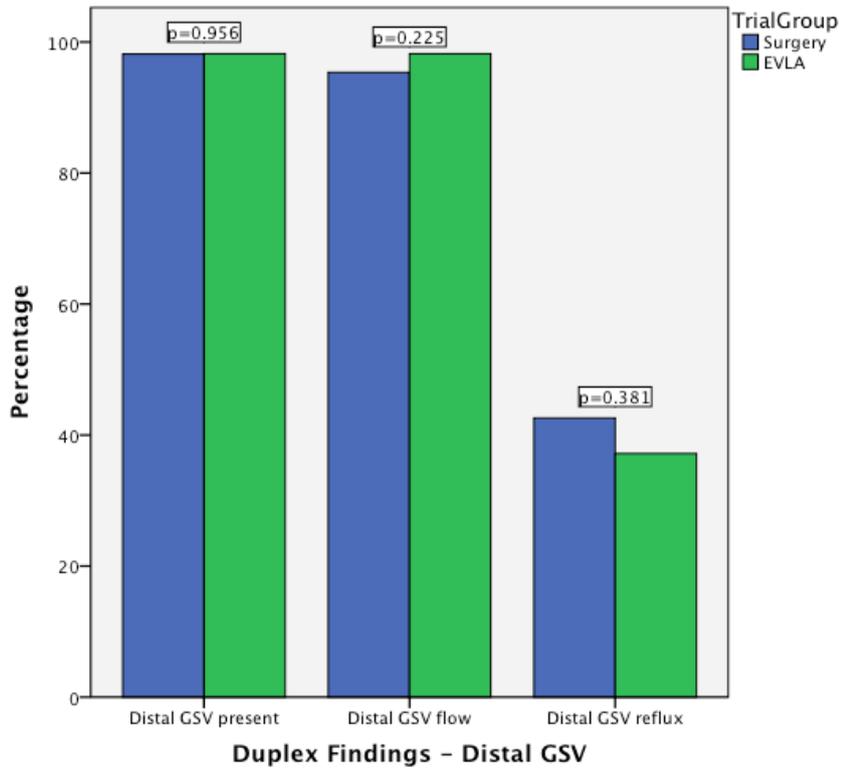
**Figure 16: DUS Characteristics of the Distal GSV at 2 years (Study 1)**

In the EVLA group, vessels that were identified on DUS but were free from flow demonstrated increased luminal echogenicity, and were non-compressible; proximal, mid- and distal GSV diameters were progressively smaller at each time-point (Figure 17, Figure 18, Figure 19, $p < 0.001$, F-A); for the purposes of this analysis, "undetected" veins were allocated a diameter of 0mm.
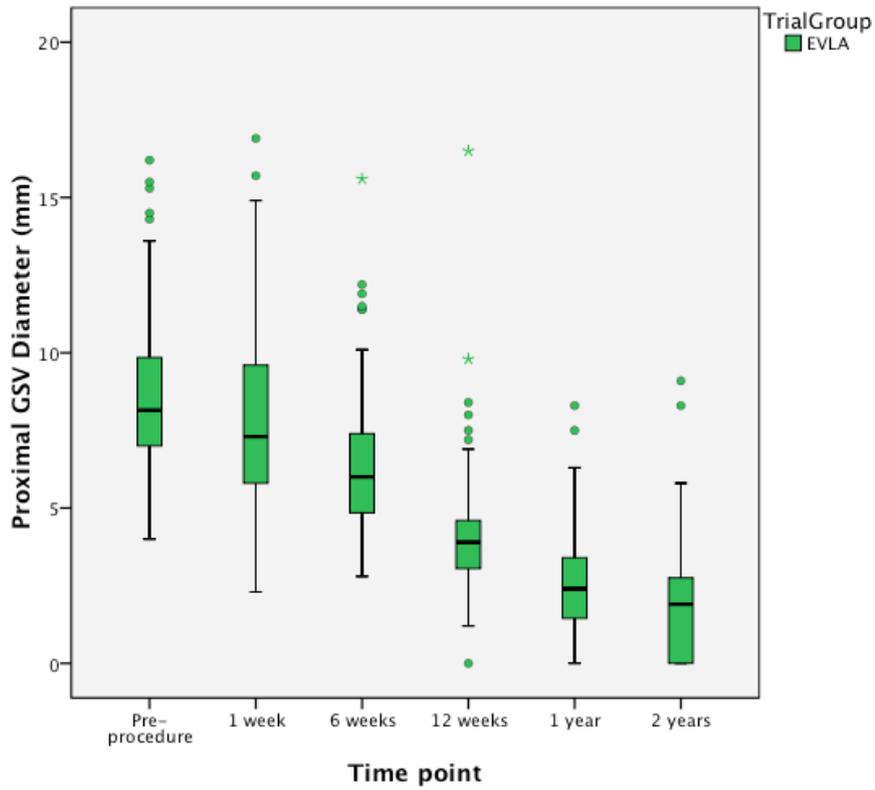
**Figure 17: Proximal GSV diameter over time in EVLA group (Study 1)**
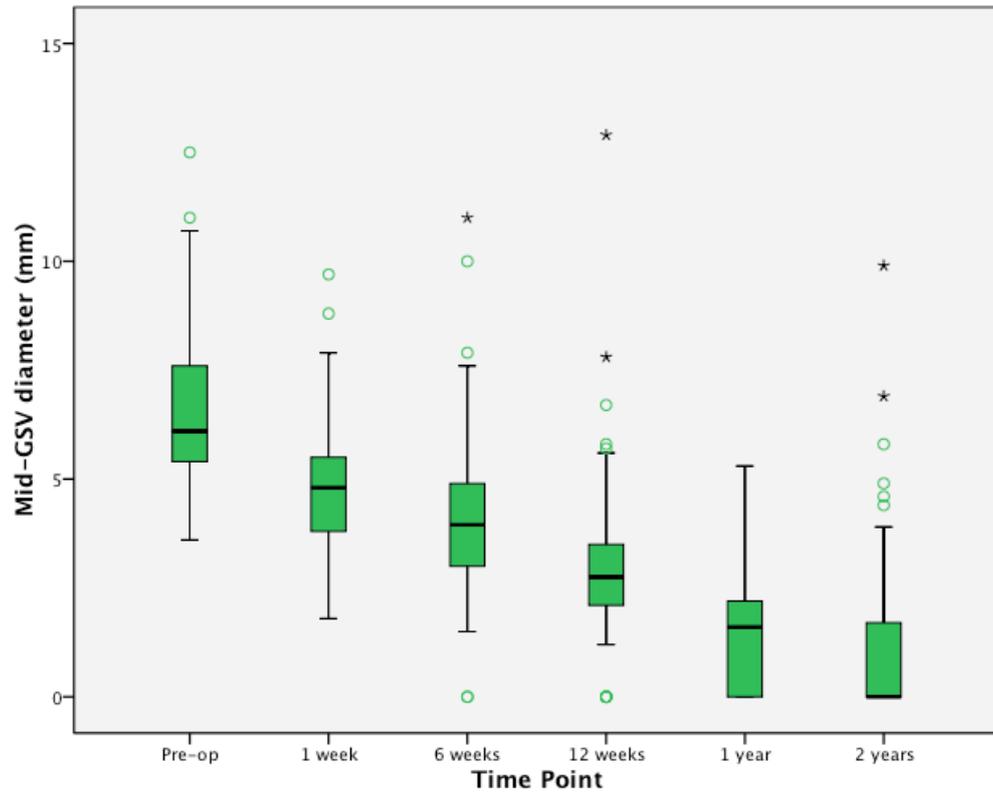


**Figure 18: Mid-GSV diameter over time in EVLA group (Study 1)**
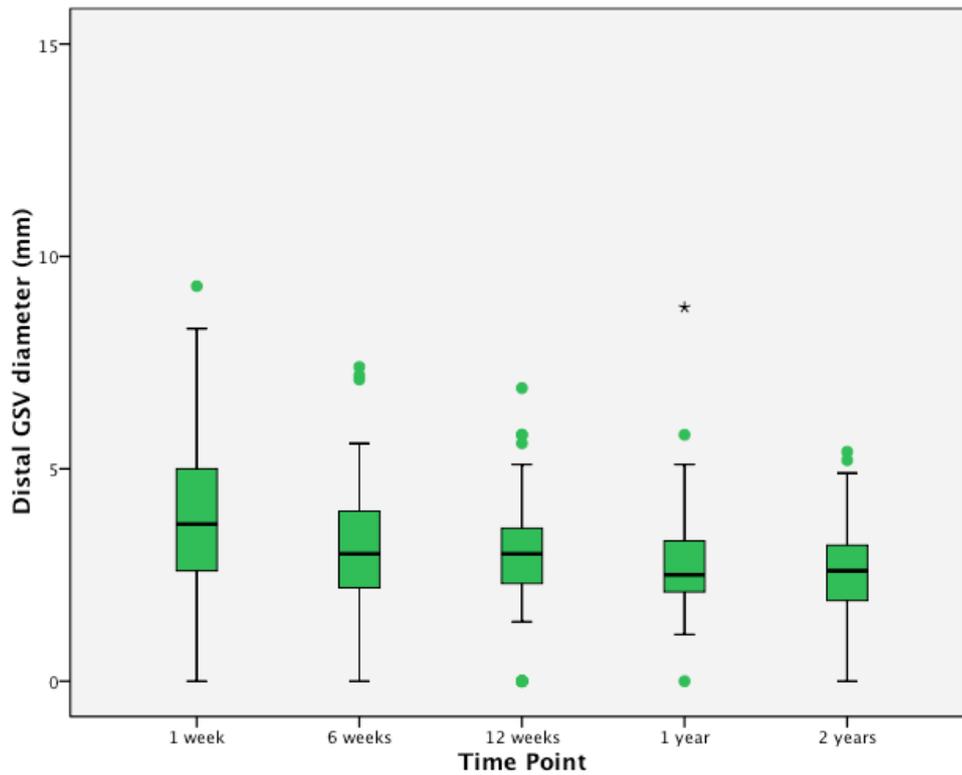
**Figure 19: Distal-GSV diameter over time in EVLA group (Study 1)**

On intragroup analysis of EVLA, there were no differences in GSV shrinkage rates between those with and without recurrence ($p>0.05$ at all time points, MWU), with significant reductions over time at the proximal- (Figure 20), mid- (Figure 21) and distal- (Figure 22) GSV ($p<0.001$, F-A).
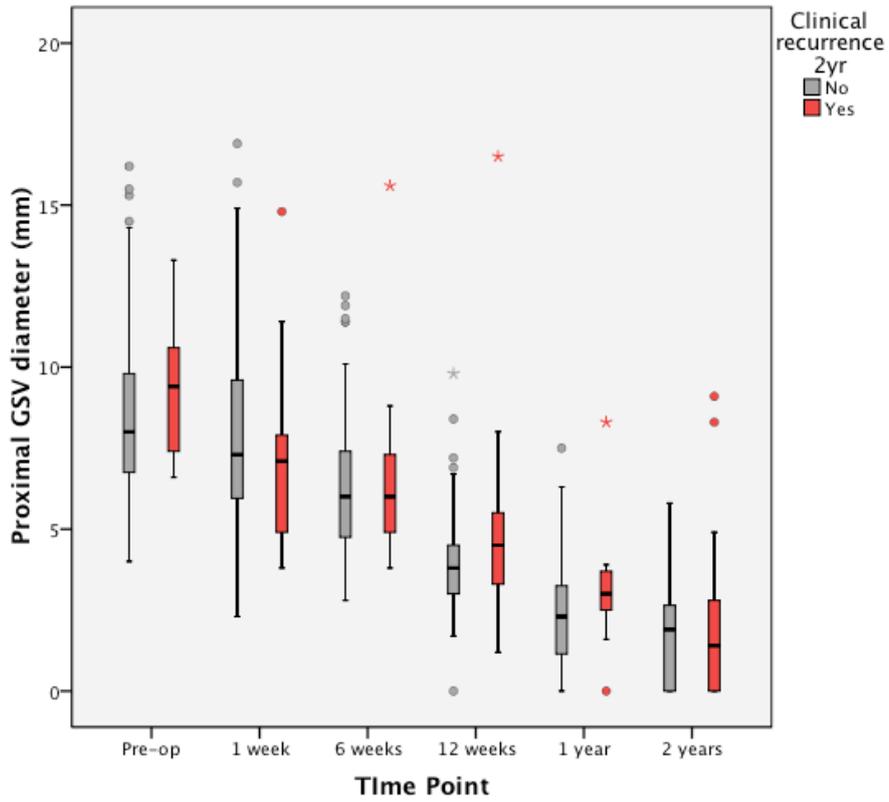
**Figure 20: Proximal GSV diameter over time in EVLA group (Clinical Recurrence versus No Recurrence) (Study 1)**
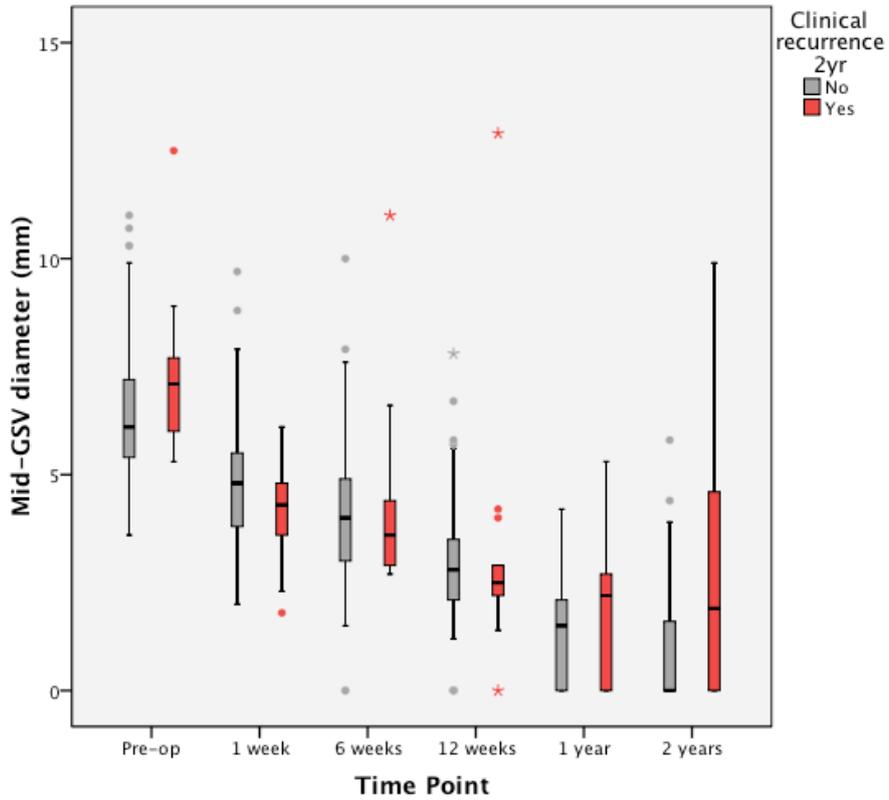


**Figure 21: Mid-GSV diameter over time in EVLA group (Clinical Recurrence versus No Recurrence) (Study 1)**
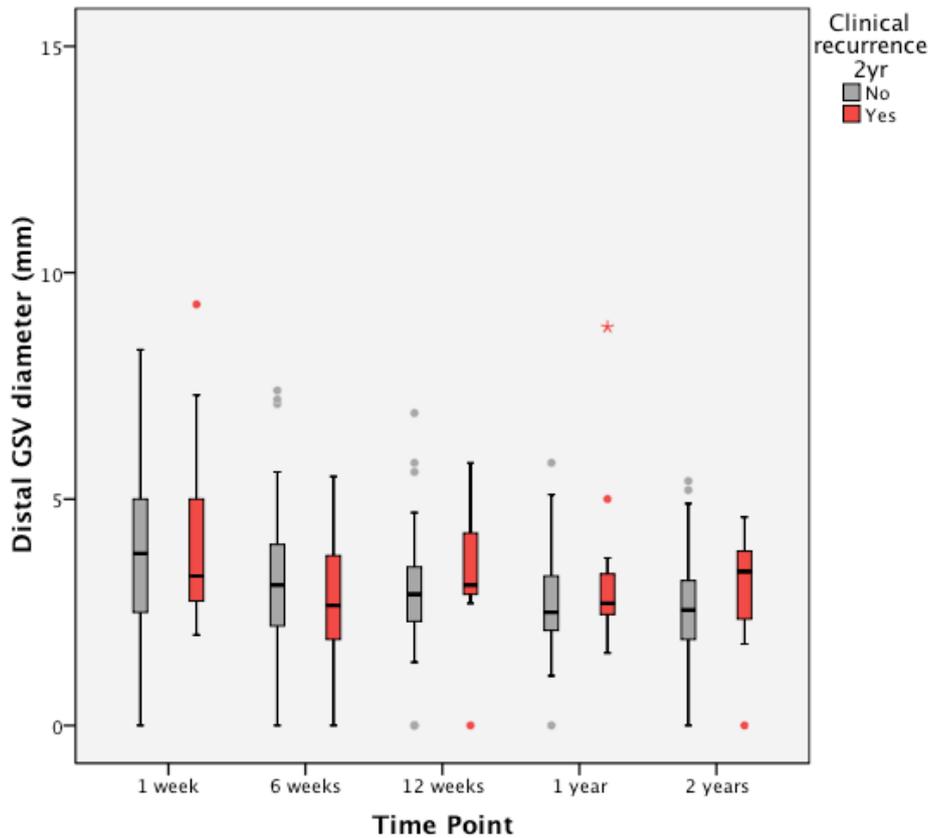
**Figure 22: Distal-GSV diameter over time in EVLA group (Clinical Recurrence versus No Recurrence) (Study 1)**

## Sub-group analysis: Clinical Recurrence – Surgery versus EVLA

In order to identify any potential targets for technique modification, patients with clinical recurrence at 2 years (n=30/111 for Surgery, n=16/116 for EVLA) were compared in a subgroup analysis for the same clinical, QoL and DUS outcomes.

Within the patients with freedom from recurrence at two years, there were no differences between the Surgery and EVLA groups for any clinical or QoL parameters

### Clinical Outcomes

Patients in the EVLA group with recurrence had similar satisfaction with the overall procedure as the surgical group with recurrence, but had significantly lower satisfaction with cosmesis (Table 10). There were no differences between the groups in terms of VCSS (Figure 23).

| | Surgery (n= 30) | EVLA (n= 16) | p* |
|---|---|---|---|
| **Patient satisfaction** | | | |
| Overall | 10.0 (8.25-10) | 9.0 (8-10) | 0.361 |
| with Cosmesis | 9.0 (7-10) | 8.0 (5-8.5) | 0.009 |
| **VCSS** | 2.0 (1-3) | 2.0 (1-3) | 0.557 |

**Table 10: Clinical Outcomes at 2 years for patients with clinical recurrence (Study 1)**

Values reported are median (iqr), *: MWU test
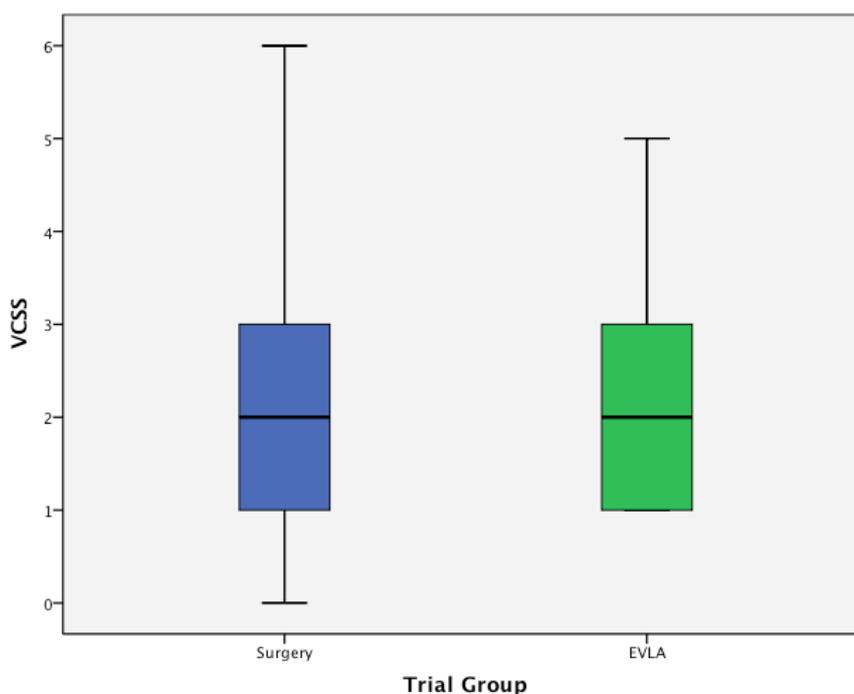


**Figure 23: VCSS at 2 years, patients with Clinical Recurrence (Study 1)**

### QoL Outcomes

Of those patients with clinical recurrence, there were no differences between the surgery and EVLA groups in any of the SF36 QoL domains (Table 11, Figure S- 4, p.273). Figure S- 5 (p.273) shows a comparison of SF36 domain scores for patients with recurrence in both groups at two years, in comparison to baseline scores.

| | Surgery (n= 30 ) | EVLA (n= 16) | p[*] |
|---|---|---|---|
| **SF36** | | | |
| Physical functioning | 95 (81.25-100) | 90 (80-100) | 0.224 |
| Role-physical | 100 (81.25-100) | 100 | 0.743 |
| Bodily pain | 84 (72.5-100) | 84 (62-100) | 0.233 |
| General Health | 82 (72-92) | 77 (72-87) | 0.533 |
| Vitality | 75 (65-83.75) | 70 (60-80) | 0.538 |
| Social functioning | 100 (87.5-100) | 100 (75-100) | 0.759 |
| Role-emotional | 100 | 100 | 0.386 |
| Mental Health | 84 (80-92) | 88 (68-92) | 0.939 |
| **EQ5D** | 1.00 (0.85-1.00) | 0.877 (0.725-1.00) | 0.026 |
| **AVVQ** | 3.961 (2-8.829) | 9.185 (5.53-13.122) | 0.037 |

**Table 11: QoL Outcomes at 2 years: Patients with Clinical Recurrence (Study 1)**

Values reported are median (iqr), [*]: MWU test

Patients in the EVLA recurrence group had significantly lower (worse) EQ5D scores and higher (worse) AVVQ scores in comparison with the surgery group at 2 years (Table 11, Figure 24 and Figure 25). The Surgery group demonstrated maintenance of the significant improvements over baseline for both EQ5D (p=0.001) and AVVQ (p<0.001) scores. The EVLA group displayed equivalent baseline and 2 years EQ5D scores (p=0.969), but maintained improvement in AVVQ scores (p=0.003).
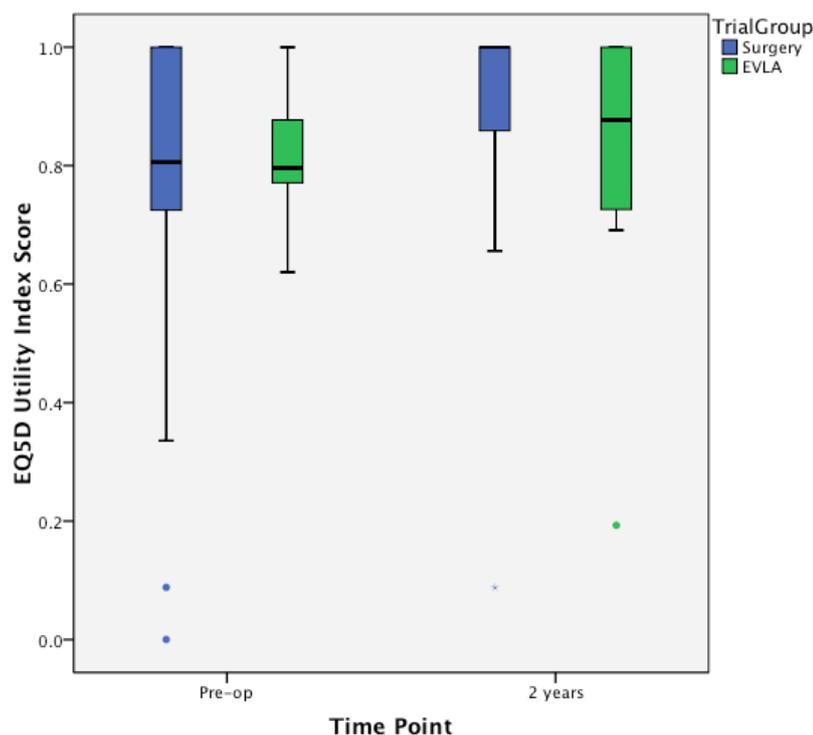


**Figure 24: EQ5D Utility Index Scores - Patients with Clinical Recurrence (Study 1)**
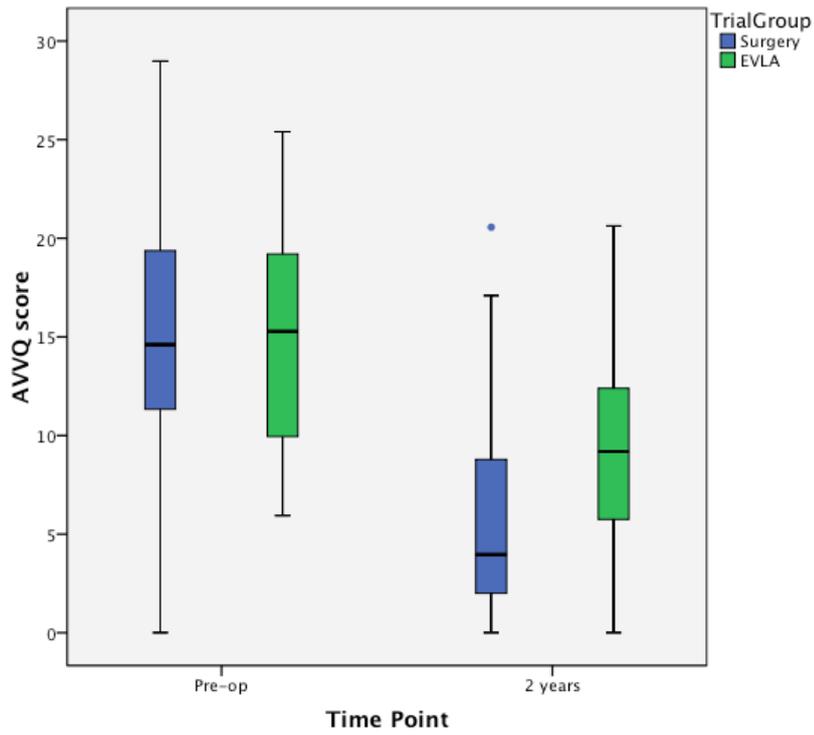
**Figure 25: AVVQ Scores - Patients with Clinical Recurrence (Study 1)**

Analysis of the raw AVVQ data suggests that the predominant cause for the difference between the surgery and EVLA group scores was based on the greater extent of varicosities drawn in question 1, rather than any great difference in symptomatology.

## DUS Patterns of Clinical Recurrence

| Group | Source of recurrence on DUS | Proportion of Clinical Recurrences |
|---|---|---|
| **Surgery** | Below-knee GSV | 17 of 30 |
| | Groin Neovascularisation | 13 of 30 |
| | Perforator: thigh | 1 of 30 |
| | Perforator: mid-calf | 8 of 30 |
| | Saphenopopliteal junction | 3 of 30 |
| | Non-axial branches alone | 3 of 30 |
| | | |
| **EVLA** | Groin tributaries | 10 of 16 |
| | Perforator: mid-calf | 6 of 16 |
| | Below-knee GSV | 4 of 16 |
| | Saphenopopliteal junction | 1 of 16 |
| | Recanalisation | 1 of 16 |
| | Non-axial branches alone | 1 of 16 |

**Table 12: Association of DUS-detected reflux with patterns of clinical recurrence (Study 1)**

Some patterns coincided; hence the combined incidence is higher than the total number of patients with recurrence.

### Surgery Group

Following surgery, clinical recurrence was most commonly due to an incompetent below-knee GSV; stripping was carried out to knee-level.  Instances of recurrence attributable to the groin (13 patients) were all related to neovascularization around the previously treated SFJ; these neo-vessels were seen to produce reflux in accessory axial trunks, which commonly reconnected with a residual GSV below the strip level. A further 11 patients had evidence of neovascularization, but without connection to any truncal reflux or clinically apparent varicosities.  Incompetent perforators (1 thigh and 8 mid-calf) were seen to contribute to GSV reflux in association with recurrent varicose veins.  Three patients developed varicosities in the Small Saphenous system, while a further three developed varicosities without any detectable truncal reflux.

On binary logistic regression analysis, both neovascularization and residual distal GSV reflux at 2 years were significant predictive factors for clinical recurrence.  Due to the small numbers involved, there were no significant predictive factors on multivariate analysis.

| Variable | B (SE) | p | Odds Ratio | 95 % CI for Odds Ratio | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Neovascularisation** | 1.086 (0.471) | 0.021 | 2.962 | 1.175 | 7.462 |
| **Residual GSV reflux (Distal) 2 years** | 1.297 (0.457) | 0.005 | 3.659 | 1.494 | 8.963 |

**Table 13: Binary Logistic regression models for predicting 2 year clinical recurrence in patients undergoing surgery (Study 1)**

Forced entry method.

### EVLA Group

Patients in the EVLA group with clinical recurrence were significantly more likely to have a patent and refluxing SFJ (p<0.001), reflux in SFJ tributaries (p<0.001), and incompetent proximal (p<0.001), mid (p<0.001) and distal (p=0.004) GSV than those without recurrence.

Ten of the 16 recurrences in the EVLA group were due to new reflux in previously competent accessory axial veins arising from a patent and incompetent SFJ; none of the patients with a flush SFJ occlusion developed this pattern of recurrence (p<0.001, $\chi^2$). There was no statistical difference in the length of vein treated (mean [SD]) (31.56cm [9.01] versus 34.17cm [10.92], (p=0.368, independent samples t-test) between EVLA recipients with and without recurrence.

All EVLA patients received a LEED of greater than 60 J/cm, with no difference between those with and without clinical recurrence (90.50Jcm$^{-1}$ [83.50-95.51] versus 94.98Jcm$^{-1}$ [85.21-104.07], p=0.303, Figure 26).
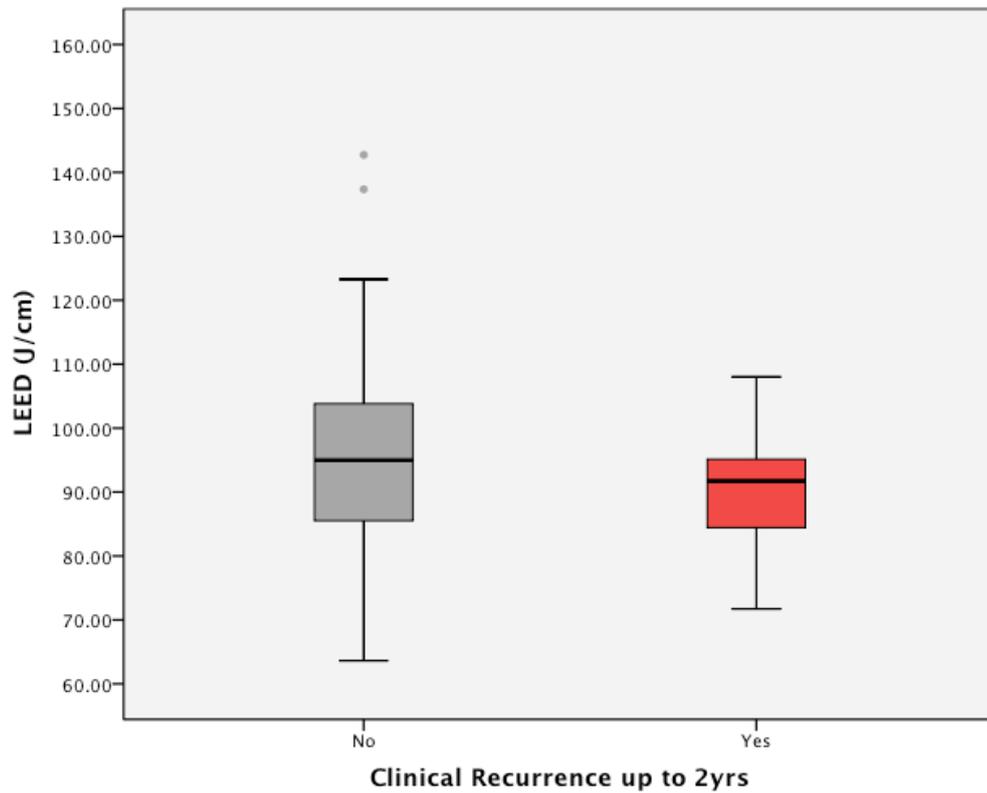
**Figure 26: LEED in EVLA patients with and without clinical recurrence (Study 1)**

However, patients with clinical recurrence attributable to groin reflux into above-knee accessory veins received a significantly lower LEED (84.3 Jcm$^{-1}$ [82.8-86.3) than those without this pattern of recurrence (94.7 Jcm$^{-1}$ [86-104.5) p=0.04 (Figure 27).
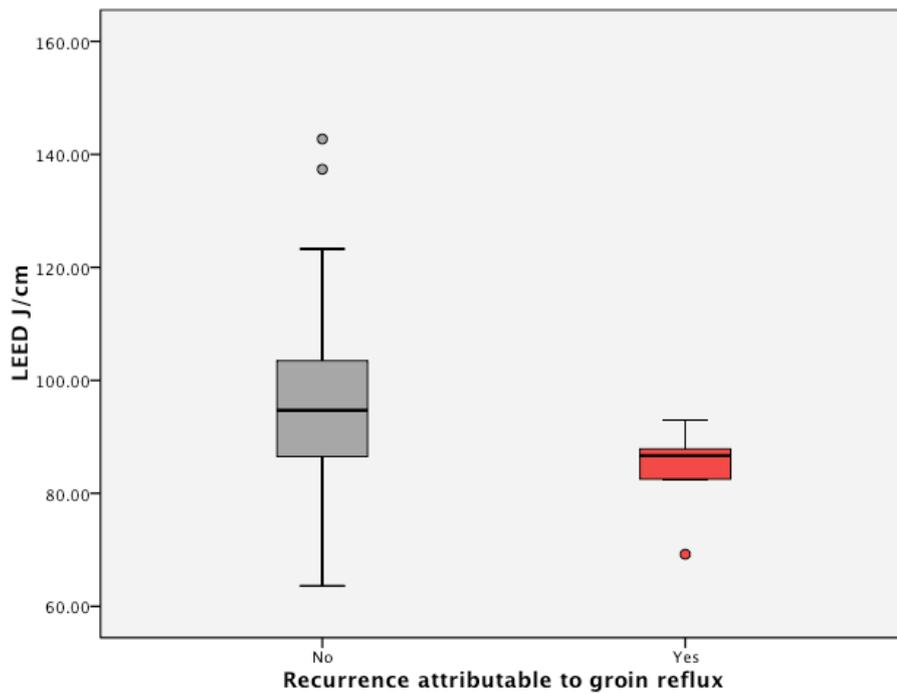
**Figure 27: LEED in EVLA patients with clinical recurrence attributable to groin reflux (Study 1)**

Of the 6 patients with evidence of refluxing mid-calf perforators in the EVLA group, none had received below-knee GSV ablation initially.

On logistic regression analysis, DUS-detected patent SFJ at both one week and 2 years, and residual GSV reflux were significant predictors of clinical recurrence at 2 years in the EVLA group (Table 14). All 5 patients who had a refluxing proximal GSV at 2 years also demonstrated an incompetent SFJ, with additional reflux in an AASV from which the clinically apparent varicosities arose. No significant predictive value was attributable to gender, height, BMI, baseline GSV diameters or LEED.

| Variable | B (SE) | p | Odds Ratio | 95 % CI for Odds Ratio | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Patent SFJ 1 week** | 1.299 (0.611) | 0.034 | 3.667 | 1.106 | 12.152 |
| **Patent SFJ 2 years** | 1.642 (0.614) | 0.008 | 5.167 | 1.550 | 17.219 |
| **Residual GSV reflux (Proximal) 2 years** | 3.466 (1.159) | 0.003 | 32.000 | 3.299 | 310.359 |
| **Residual GSV reflux (Mid) 2 years** | 2.656 (0.797) | 0.001 | 14.242 | 2.988 | 67.892 |
| **Residual GSV reflux (Distal) 2 years** | 1.559 (0.581) | 0.007 | 4.755 | 1.521 | 14.862 |

**Table 14: Binary Logistic regression models for predicting 2-year clinical recurrence in patients undergoing EVLA (Study 1)**

Forced entry method.


# Treatments for Recurrent Varicose Veins

Only two patients (one in each treatment group) with recurrence attributable to below-knee GSV reflux were unsuitable for EVLA, due to excessive tortuosity; they successfully underwent UGFS.

As stated earlier, one patient attended 2-year follow-up after failing to attend at one year. This patient had been randomized to EVLA, and had developed recurrent varicosities in the GSV distribution. The patient was noted on preoperative DUS to have a duplex left GSV system (anterolateral and posteromedial branches arising from the SFJ, both passing within the saphenous fascia down the thigh and into the calf). The posteromedial vein was noted to be competent, small calibre and without any associated varicosities; this vein was therefore not treated. The anterolateral vein was incompetent throughout its length from the SFJ, causing reflux into clinically evident varicosities. The patient underwent successful EVLA of the anterolateral vein. At 1, 6 and 12-week follow-up, the posteromedial vein was still small and competent, while the anterolateral vein remained fully ablated. The SFJ was competent, with a patent but competent proximal GSV segment. At two-year follow-up, the patient complained of clinically evident GSV varicosities, which on DUS were identified as arising from the untreated posteromedial GSV that had developed reflux from a now incompetent SFJ. The patient was offered the choice of either EVLA or surgery; they opted for surgery.

All other patients undergoing treatment for incompetent axial veins opted to receive EVLA either alone, or in combination with ambulatory phlebectomy or foam sclerotherapy. Patients with recurrent varicosities without axial reflux underwent ambulatory phlebectomy alone.

## 3.2 Study 2:  Buffering of Tumescent anaesthesia: finding the optimum solution

As planned, 3 runs of 3 pH tests were performed for each solution. Table 15 shows the mean (SD) pH results for each of the solutions under test; the pH of each tumescent solution was significantly different to that of any other solution (Figure 28).

| | Solution | pH | p |
|---|---|---|---|
| | 0.9% NaCl | 6.55 (0.02) | |
| | 1% Lidocaine | 6.46 (0.01) | |
| | 1% Lidocaine + 1:200,000 Epinephrine | 4.38 (0.01) | |
| | 2% Lidocaine + 1:200,000 Epinephrine | 4.58 (0.01) | |
| Tumescent Anaesthetic Solution | A | 6.32 (0.01) | |
| | B | 7.09 (0.01) | |
| | C | 7.11 (0.01) | |
| | D | 7.22 (0.01) | p<0.001[*] |
| | E | 7.30 (0.01) | |
| | F | 7.40 (0.01) | |
| | G | 7.59 (0.01) | |

**Table 15: pH analyses (Study 2)**

pH reported as mean (SD). Analyses performed at 21°C+/-0.5°C
Tumescent Anaesthetic Solution = 0.1% Lidocaine + 1:2000,000 Epinephrine plus:

**A**: Plain.   **B**: 2ml 8.4% $NaHCO_3$.   **C**: 4ml 8.4% $NaHCO_3$.   **D**: 6ml 8.4% $NaHCO_3$.   **E**: 8ml 8.4% $NaHCO_3$

**F**: 10ml 8.4% $NaHCO_3$.   **G**: 12ml 8.4% $NaHCO_3$.   *: Independent samples students t-test
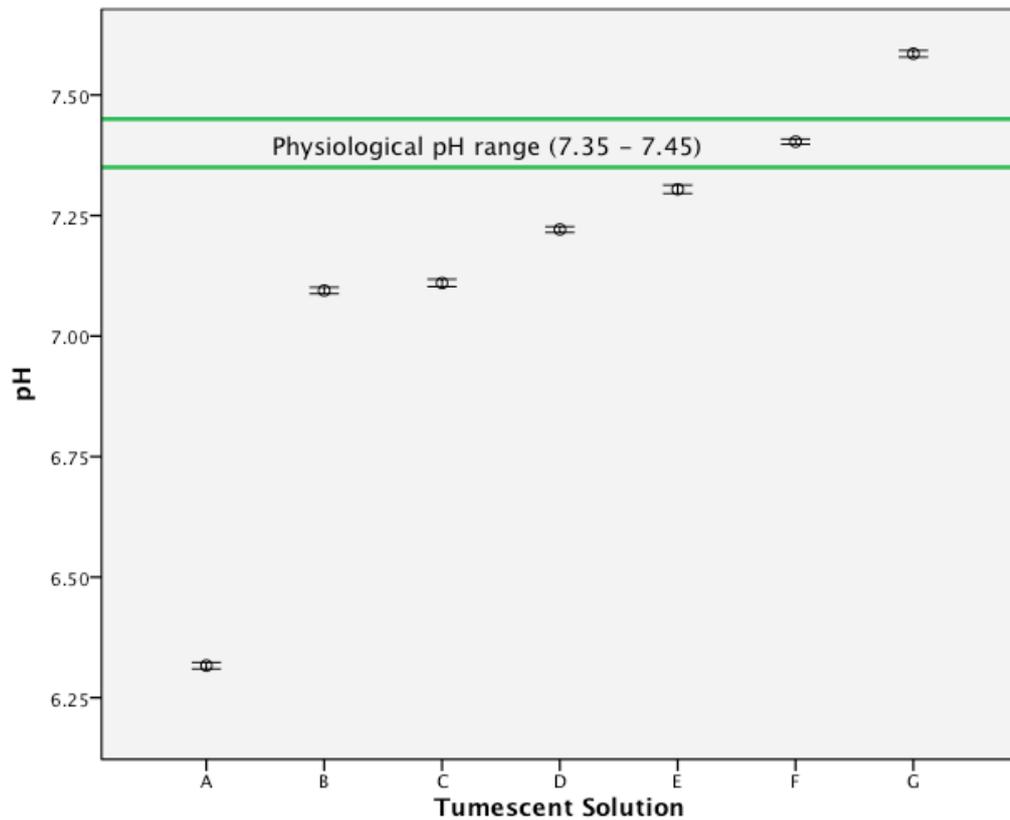
**Figure 28: pH of tumescent anaesthetic solutions with increasing quantities of 8.4% NaHCO₃ (Study 2)**

Tumescent Anaesthetic Solution = 0.1% Lidocaine + 1:2000,000 Epinephrine plus:

**A**: Plain.  **B**: 2ml 8.4% $NaHCO_3$.  **C**: 4ml 8.4% $NaHCO_3$.  **D**: 6ml 8.4% $NaHCO_3$.  **E**: 8ml 8.4% $NaHCO_3$

**F**: 10ml 8.4% $NaHCO_3$.  **G**: 12ml 8.4% $NaHCO_3$.

Based on these data, solution F (0.1% Lidocaine + 1:2000,000 Epinephrine plus 10ml 8.4% $NaHCO_3$) provided the optimum, most "physiological" pH and was taken forward as the solution of choice for Study 3.

## 3.3 Study 3: Cohort study of Buffered versus unbuffered Tumescent anaesthesia in EVLA

A cohort of 31 consecutive patients underwent 810nm, 14W continuous EVLA plus AP under local tumescent anaesthesia, buffered to physiological pH (Solution F from Study 2). These patients were compared to a previous cohort of patients receiving the same treatment. There were no differences between the groups in terms of baseline characteristics for clinical (Table 16), QoL (Table 17) or DUS (Table 18) features.

| Clinical Characteristics | | Unbuffered n=31 | Buffered n=31 | p value |
|---|---|---|---|---|
| Age (years) | | 54 (14.8) | 49 (18) | 0.194 |
| Female sex | | 15/31 | 21/31 | 0.123 |
| Left leg | | 13/31 | 19/21 | 0.127 |
| BMI (kgm$^{-2}$) | | 26.31 (24.54-29.71) | 30.01 (27.82-32.87) | 0.794 |
| VCSS | | 5 (4-7) | 5 (4-6) | 0.542 |
| CEAP Clinical Grade | C2 | 17 | 20 | |
| | C3 | 0 | 4 | |
| | C4 | 13 | 6 | 0.078 |
| | C5 | 1 | 1 | |
| | C6 | 0 | 0 | |

**Table 16: Baseline Clinical Characteristics (Study 3)**

| QoL Characteristics | Unbuffered | Buffered | p value |
|---|---|---|---|
| SF36 | | | |
| Physical Functioning | 95 (70-100) | 90 (70-100) | 0.669 |
| Role-physical | 100 (50-100) | 100 (0-100) | 0.649 |
| Bodily pain | 72 (51-100) | 67 (41-84) | 0.144 |
| General Health | 72 (60-82) | 72 (57-83.25) | 0.817 |
| Vitality | 70 (50-85) | 70 (43.75-85) | 0.482 |
| Social Functioning | 100 (75-100) | 93.75 (62.5-100) | 0.279 |
| Role-emotional | 100 (66-100) | 100 | 0.517 |
| Mental Health | 88 (60-92) | 88 (72-92) | 0.884 |
| EQ5D | 0.806 (0.796-1.000) | 0.796 (0.620-1.000) | 0.068 |
| AVVQ | 12.00 (8.97-15.54) | 14.28 (9.99-19.10) | 0.160 |

**Table 17: Baseline QoL Characteristics (Study 3)**

| DUS Characteristics | | Unbuffered | Buffered | p value |
|---|---|---|---|---|
| SFJ Reflux | | 31/31 | 31/31 | 1.00 (FET) |
| GSV diameter | Prox | 9.0 (7.4-10.1) | 8.5 (6.8-11.6) | 0.688 |
| (mm) | Mid | 7.0 (5.3-8.6) | 5.9 (4.4-8.0) | 0.276 |

**Table 18: Baseline DUS Characteristics (Study 3)**

All patients attended scheduled follow-up up to 12 weeks.

## Clinical Outcomes

### *Periprocedural*

All patients underwent the planned procedure (31 patients in each treatment group). There were no differences between the groups in terms of key treatment data (Table 19)

| Treatment Data | Unbuffered | Buffered | p value |
|---|---|---|---|
| Length of vein treated (cm) | 51.0 (34-58) | 44.5 (38.5-59.3) | 0.941 |
| Volume of tumescent anaesthesia (ml) | 800 (700-937) | 775 (575-925) | 0.285 |
| LEED ($Jcm^{-1}$) | 106 (92-120.9) | 99 (73.4-121) | 0.198 |

**Table 19: Key treatment data (Study 3)**

Periprocedural pain, stated on patient-reported 10cm VAS at the conclusion of the procedure, was significantly lower in the patients receiving Buffered anaesthetic (median 1 [iqr 0.25-2.25] versus 4 [3-6], p<0.001, Figure 29).
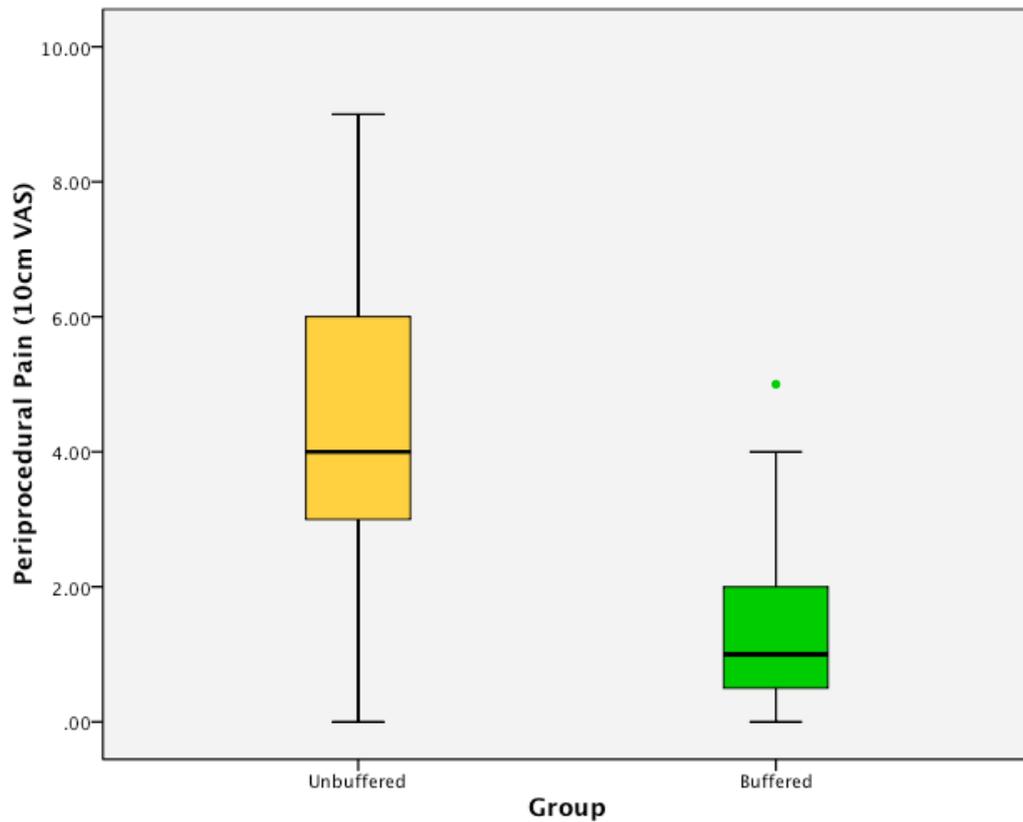
**Figure 29 Periprocedural pain (Study 3)**

Figure 30 shows ROC Area under the Curve analysis, which was undertaken to assess the predictive strength of less pain indicating treatment using Buffered anaesthesia. AUC=0.819 (95% CI: 0.702-0.936), p<0.001; indicating a very strong predictive value of lower periprocedural pain designating treatment in the Buffered group.
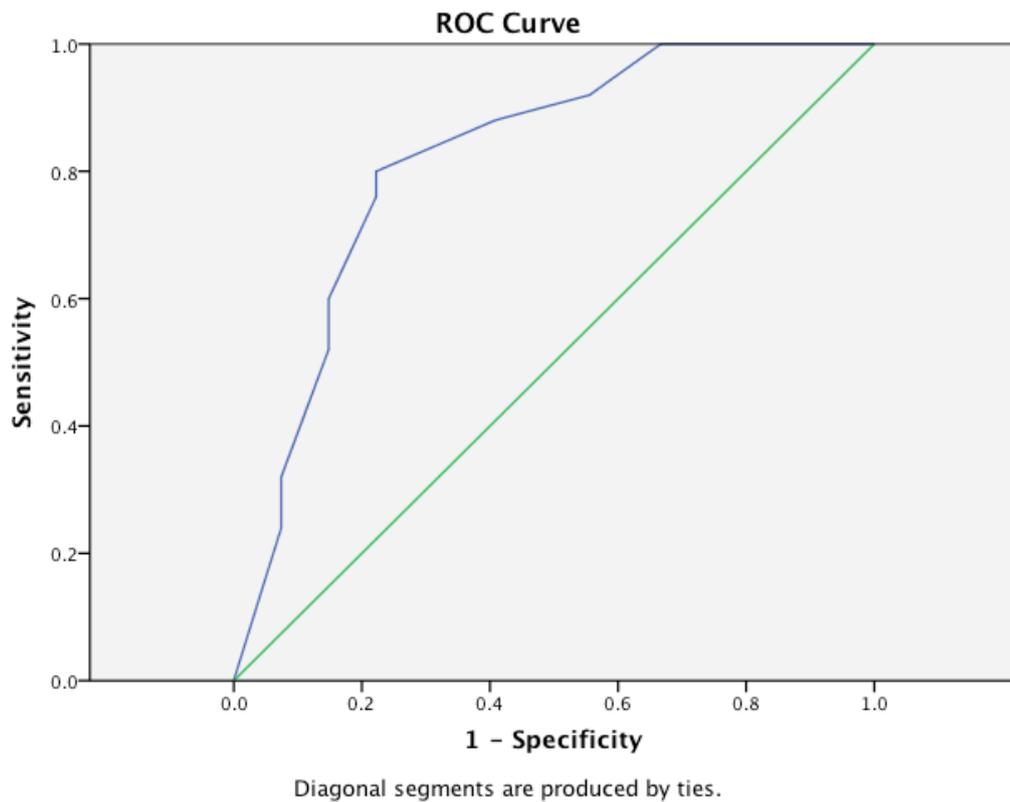
**Figure 30: ROC for patient-reported peri-procedural pain (Study 3)**

AUC=0.819 (95% CI: 0.702-0.936), p<0.001.

## Sex-differences in Pain reporting

There was a trend to females reporting higher pain scores in both groups; this reached statistical significance in the Unbuffered group (p=0.029, Figure 31), but not in the Buffered group (p=0.109, Figure 32). Both sexes reported significantly lower pain scores in the Buffered anaesthesia group compared to the Unbuffered group (p<0.005, MWU).
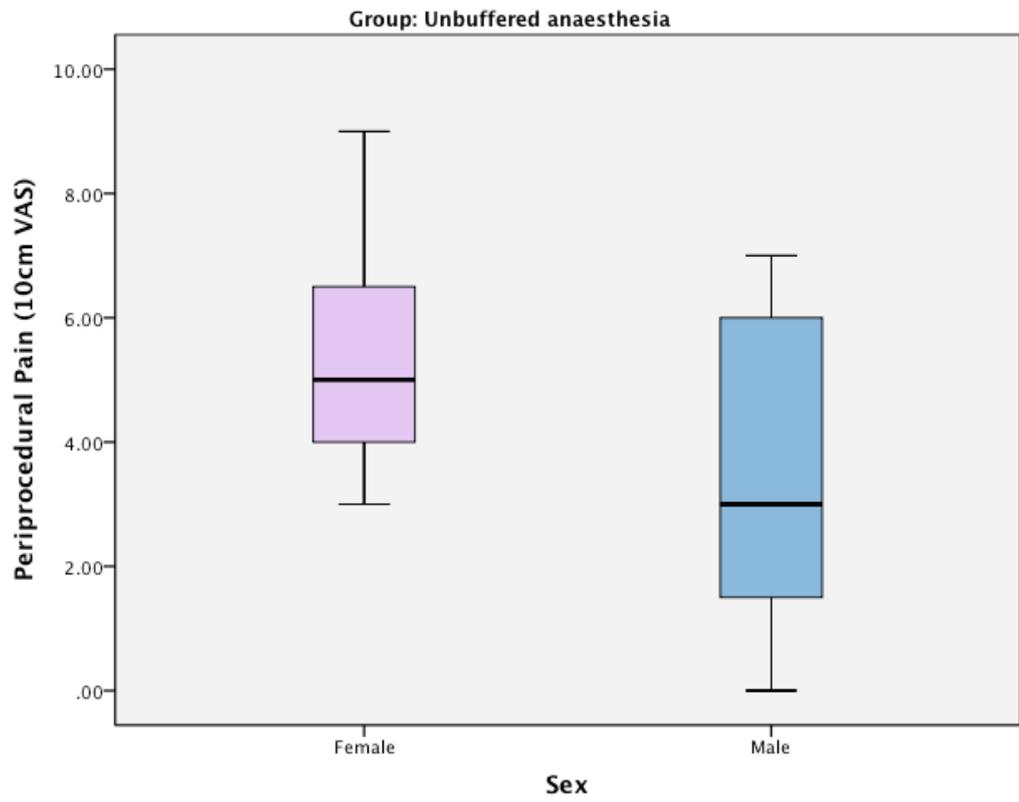
**Figure 31: Sex differences in periprocedural pain reporting (Unbuffered anaesthesia)**
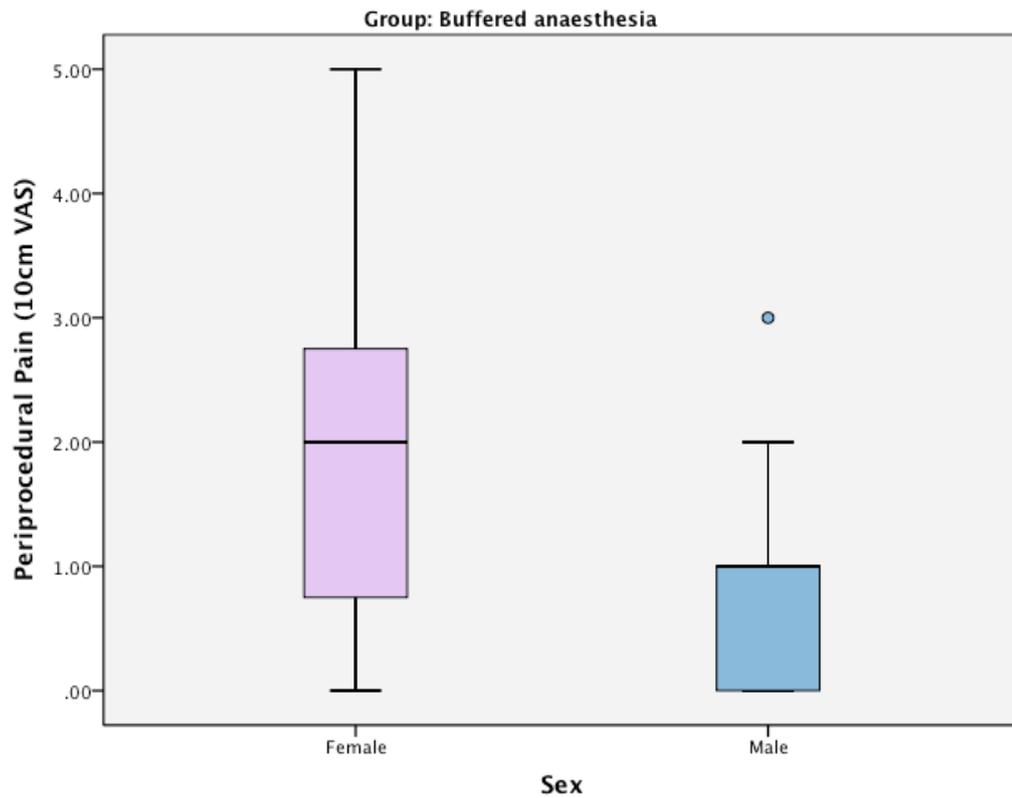
**Figure 32: Sex differences in periprocedural pain reporting (Buffered anaesthesia)**

*Postprocedural*

Pain

The lower periprocedural pain in the Buffered group also translated into lower pain scores at the end of the treatment day (day 0), with a median (iqr) score of 1.8 (0.3-2.8) versus 3.0 (1.2-5.2) for the Unbuffered cohort (p=0.033, MWU). There were no differences between the pain scores at any other time point (Figure 33).
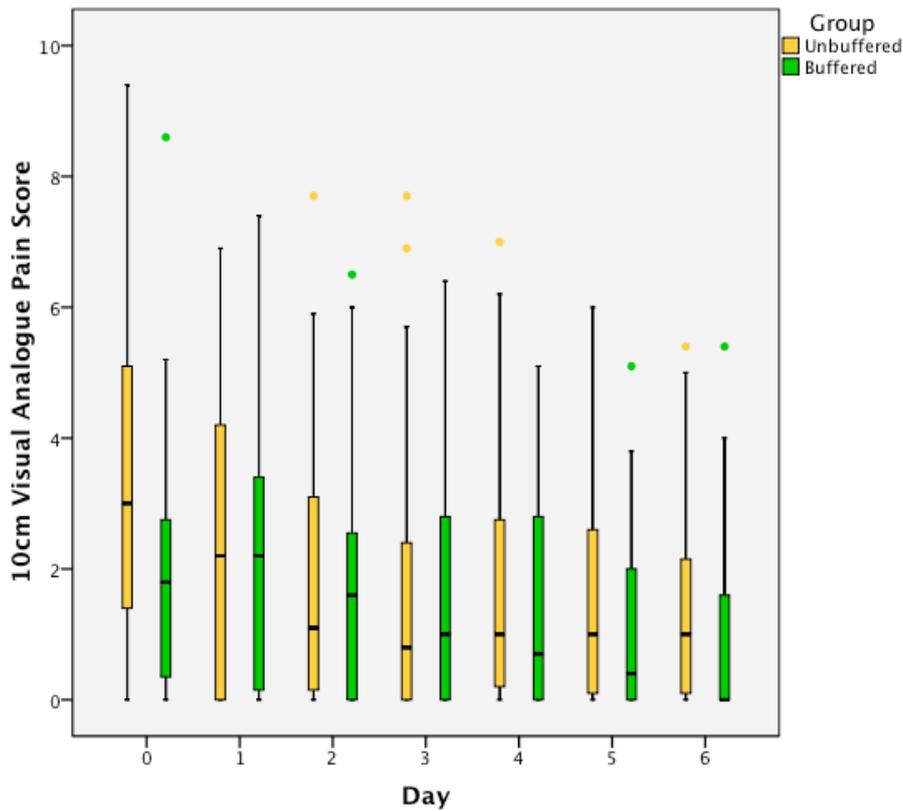
**Figure 33: Patient-reported post-procedural pain (Study 3)**

## Complications

Complication rates were low in both groups (Table 20).

| Complication | Unbuffered | Buffered | p value |
|---|---|---|---|
| Infection | 0 | 0 | N/A |
| VTE/eHIT | 0 | 0 | N/A |
| Superficial thrombophlebitis | 0 | 0 | N/A |
| Sensory disturbance | 2 | 1 | 1.00 (FET) |
| Skin staining | 1 | 0 | 1.00 (FET) |

**Table 20: Post-procedural Complications (Study 3)**

At 12 weeks, two patients in each group had residual varicosities. In the Unbuffered anaesthesia group, one patient chose to undergo further ambulatory phlebectomy, while the other opted for conservative management. Both patients in the Buffered group chose to undergo ambulatory phlebectomy.

## Time to resume normal activities

There was no difference between the treatment groups in the time taken to resume normal activities (p=0.541, Figure 34)
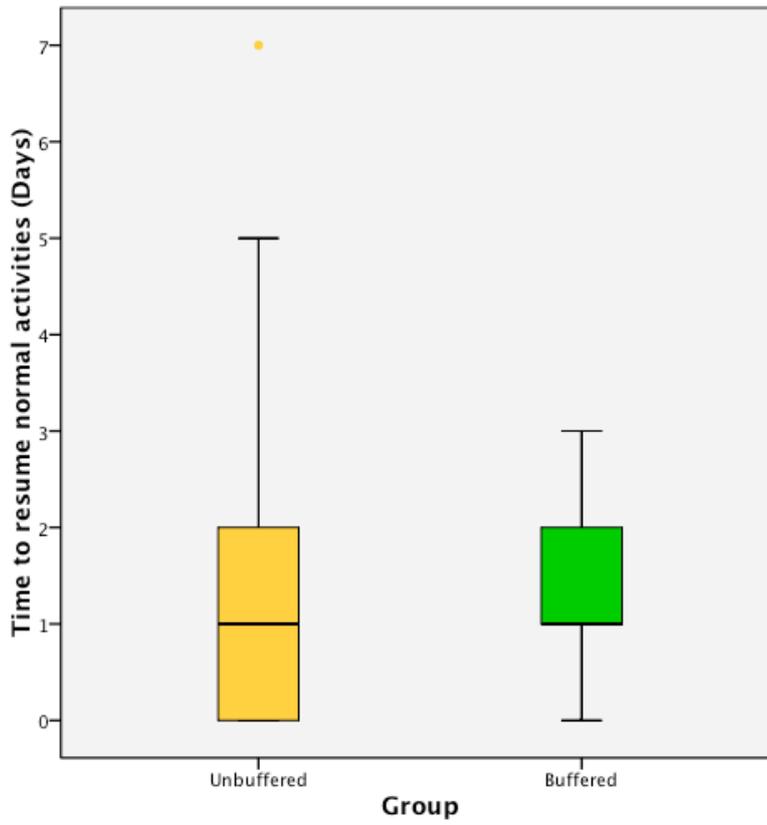


**Figure 34: Time to resume normal activities (Study 3)**

## Patient Satisfaction

Patient satisfaction with both the overall treatment experience and with cosmesis was high in both groups, with no significant differences (p=0.113 and p=0.207, respectively) (Figure 35)
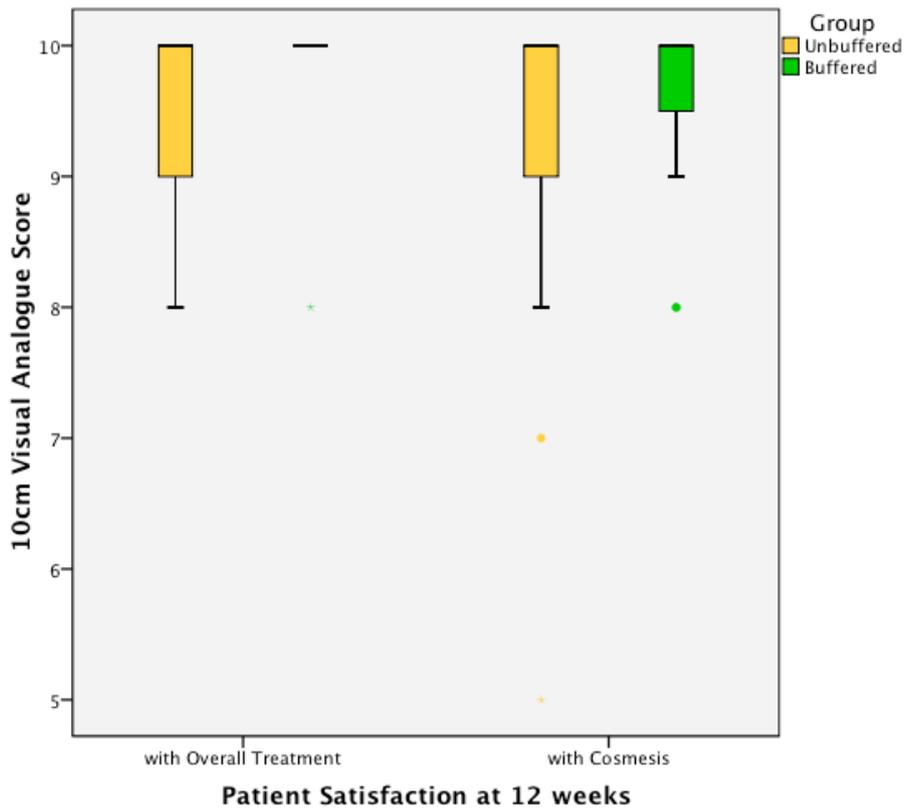
**Figure 35: 12-week patient satisfaction scores (Study 3)**

VCSS

Both groups demonstrated significant improvements in 12 week VCSS over baseline ($p<0.001$ for both the Unbuffered and Buffered groups, WSR). There was a trend toward slightly lower (better) 12-week VCSS in the Buffered group (Figure 36), but this did not reach statistical significance ($p=0.063$), and would be of little clinical significance.
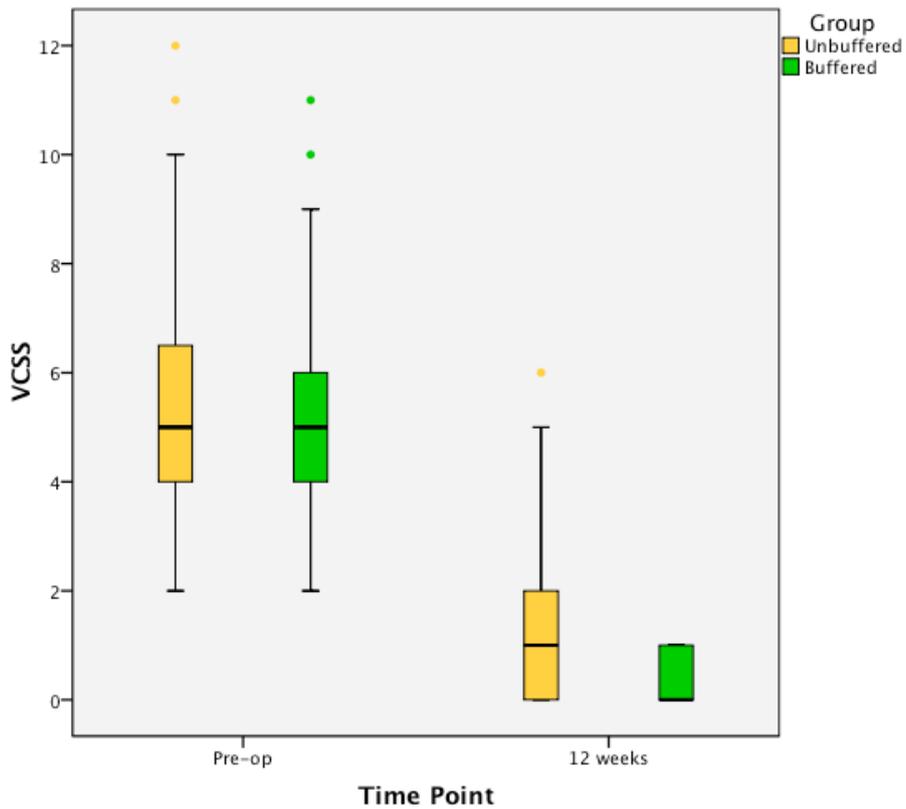
**Figure 36: VCSS over time by group (Study 3)**

## QoL Outcomes

Figure S- 6, p.277, displays the SF36 domain scores for the Unbuffered and Buffered groups from baseline to 12-week follow-up.

### *SF36 Domains – Intergroup analysis, Unbuffered versus Buffered anaesthesia*

On intergroup analysis, there were no significant differences between the groups at any time point, with the exception of a modestly higher (better) score at 6 weeks for the domain of Bodily Pain in the Unbuffered group (p=0.034); this is likely to be Type 1 error.

### SF36 Domains – Intragroup analysis

#### Unbuffered anaesthesia

Intragroup analysis (WSR test) in the Unbuffered group identified significant deterioration in the domains of Physical Functioning (p=0.038) and Bodily pain (p=0.004) from baseline to 1 week. There were no differences between baseline and 1 week in the other domain scores (R-P, p=0.472; GH, p=0.310; Vit, p=0.372; SF, p=0.605; R-E, p=0.470; MH, p=0.913).

At 6 weeks, there were no differences from baseline for any of the SF36 domains, with the exception of modest improvements in Social Functioning and Mental Health scores (PF p=0.335; R-P p=0.325; BP p=0.096; GH p=0.221; Vit p=0.208; SF p=0.048; R-E p=0.143; MH p=0.043)

At 12 weeks, the Unbuffered group had significantly improved SF36 domain scores for Bodily pain (p=0.009) and Role-physical (p=0.05). There were no differences over baseline scores for the other domains (PF p=0.161; GH (p=0.486); Vit p=0.749; SF p=0.058; R-E p=0.157; MH p=0.895).

#### Buffered anaesthesia

Compared to baseline scores, there were no changes to the SF36 domain scores at 1 week, with the exception of a fall in Social Functioning scores (PF p=0.330; R-P p=0.765; BP p=0.106; GH p=0.190; Vit p=0.828; SF p=0.036; R-E p=0.223; MH p=0.209).

At 6 weeks, there were significant improvements over baseline for domain scores in PF (p=0.019), R-P (p=0.014), BP (p=0.023) and Vit (p=0.014). The improvements in scores for SF (p=0.054) approached statistical significance. There were no differences over baseline in the 6-week scores for GH (p=0.099), R-E (p=0.301) or MH (p=0.181).

At 12 weeks, there were sustained significant improvements over baseline in the scores for PF (p=0.034), BP (p=0.013), GH (0.010), Vit (p=0.012) and MH (p=0.004). The domain scores for R-P (p=0.059), SF (p=0.916), R-E (p=0.655) were not significantly different to baseline.

On Friedman's ANOVA testing, QoL improvement over time was significant for the domain scores in Physical Functioning (Unbuffered, p<0.001; Buffered, p=0.048), Role-physical (Unbuffered, p=0.046; Buffered, p=0.029); Bodily Pain (Unbuffered, p<0.001; Buffered, p=0.035) and Social Functioning (Unbuffered, p=0.011; Buffered, p=0.010).

### *EQ5D Utility Index Scores*

Figure 37 shows the changes in EQ5D score over time in each treatment group. On intergroup analysis, there were no differences between the groups at any time point from baseline to 12 weeks (p=0.068, 0.477, 0.557 and 0.393 respectively).
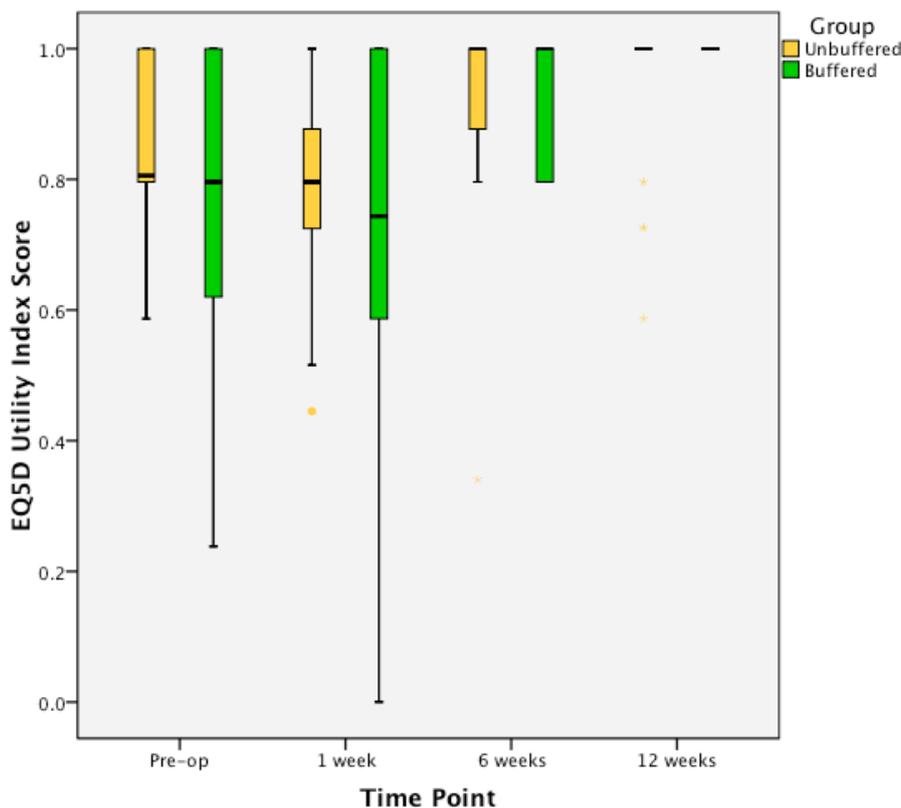


**Figure 37: EQ5D Utility Index Scores over time (Study 3)**

Intragroup analysis identified a significant deterioration in 1-week scores over baseline in the Unbuffered group (p=0.031), while the Buffered group scores were not statistically different (p=0.758). At 6 weeks, both groups displayed improvements over baseline, although not statistically significant (p=0.073 and p=0.059 respectively). By 12 weeks, both groups had significantly improved EQ5D scores over baseline (Unbuffered p=0.004l, Buffered p<0.001).

The trends to improved EQ5D scores over time were significant on Friedman's ANOVA analysis (Unbuffered, p<0.001; Buffered, p=0.039).

### AVVQ

There were no intergroup differences at 1 week or 12 weeks, however there was a higher (median [iqr]) AVVQ score at 6 weeks in the Buffered anaesthesia group (8.11 [3.73-16.12] compared to the Unbuffered anaesthesia group (4.5 [0.906-8.216]), p=0.016 (Figure 38).
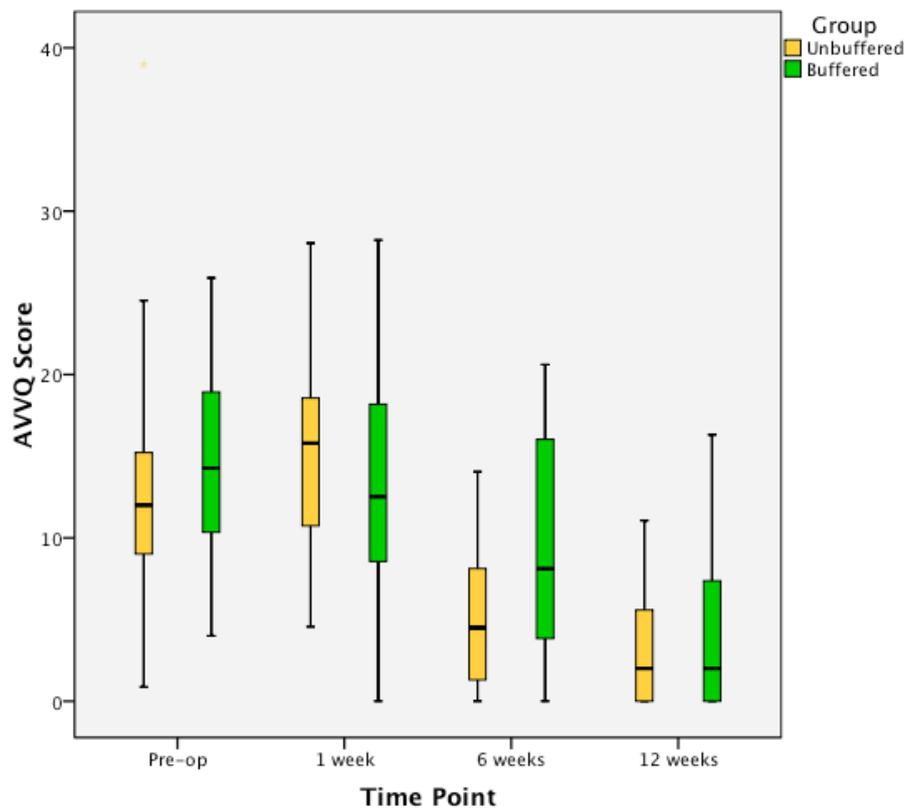


**Figure 38: AVVQ scores over time (Study 3)**

On intragroup analysis, there was no significant change in AVVQ at 1 week in either group (Unbuffered p=0.127, Buffered p=0.096), followed by improvements over baseline scores at both 6 weeks (Unbuffered p<0.001, Buffered p=0.002) and 12-week (both groups p<0.001). The improved scores over time were significant in both groups (p<0.001, F-A)

## DUS Outcomes

All patients had successful eradication of reflux in the treated GSV at 1week, with no cases of recanalization over the 12-week follow-up period. A flush SFJ occlusion was seen in 19 of 31 and 18 of 31 patients in the Unbuffered and Buffered groups respectively at 1 week. These findings were maintained at 12 weeks, with both groups also demonstrating significant shrinkage of the treated GSV over time ($p < 0.001$, F-A), with no differences between the groups ($p < 0.05$ at all time points, MWU).
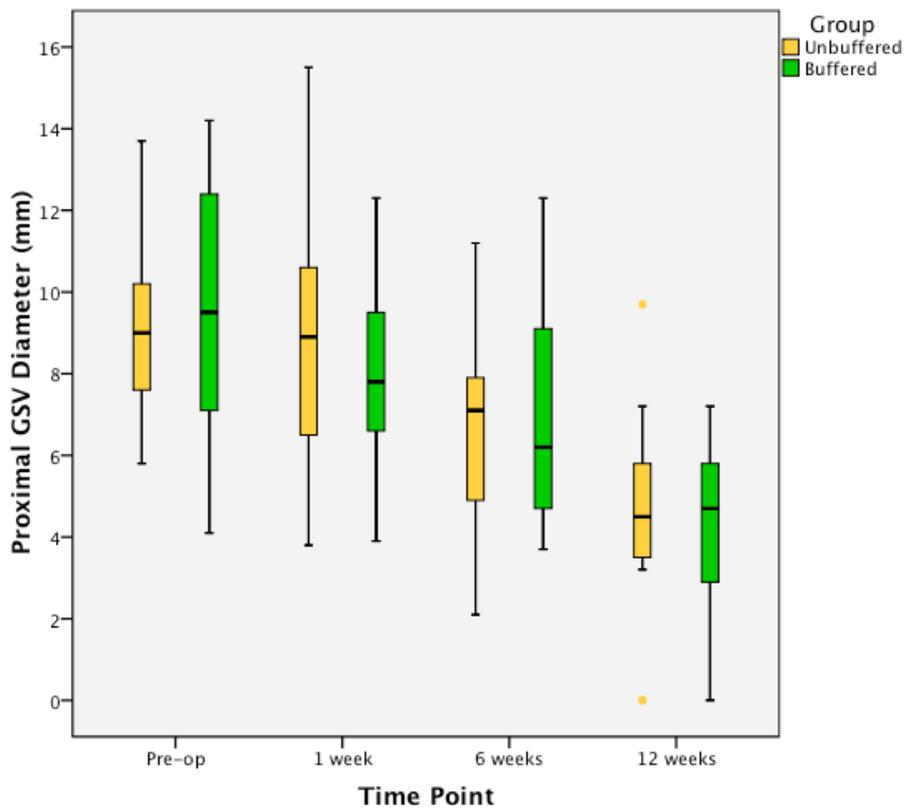


**Figure 39: Proximal GSV diameter over time (Study 3)**
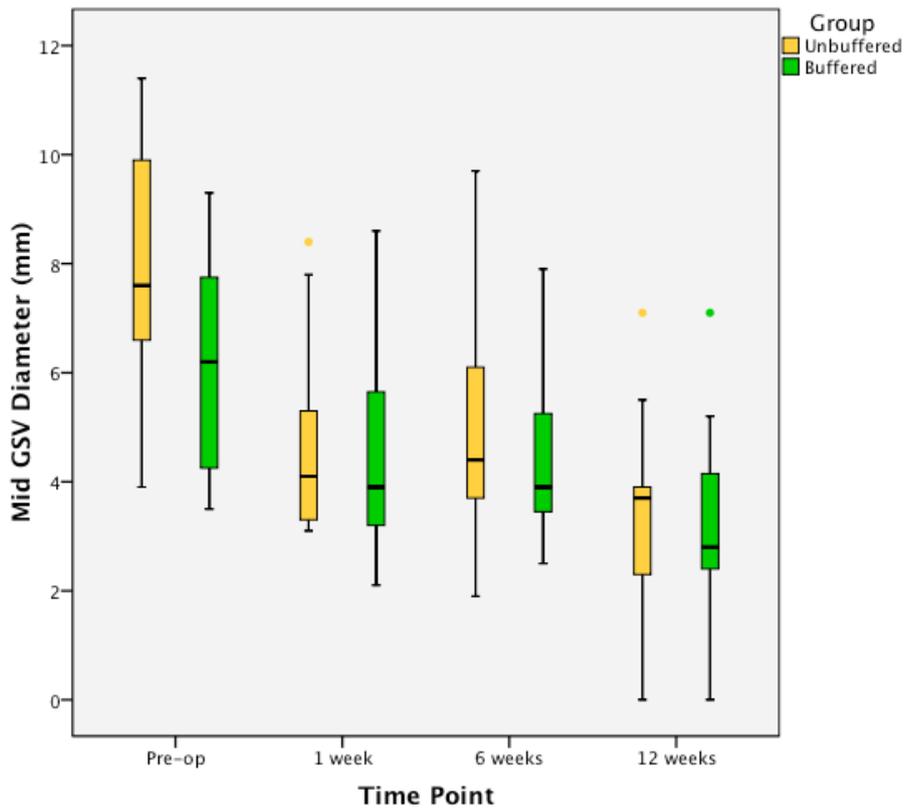
**Figure 40: Mid-GSV diameter over time (Study 3)**

Comparing those with and without a successful flush SFJ occlusion revealed no differences in BMI (median [iqr] 25.5[24.7-30.2] versus 28.4[26.2-32.3], p=0.227), proximal GSV diameter (p=0.242, Figure 41) or the LEED delivered (p=0.766, Figure 42).
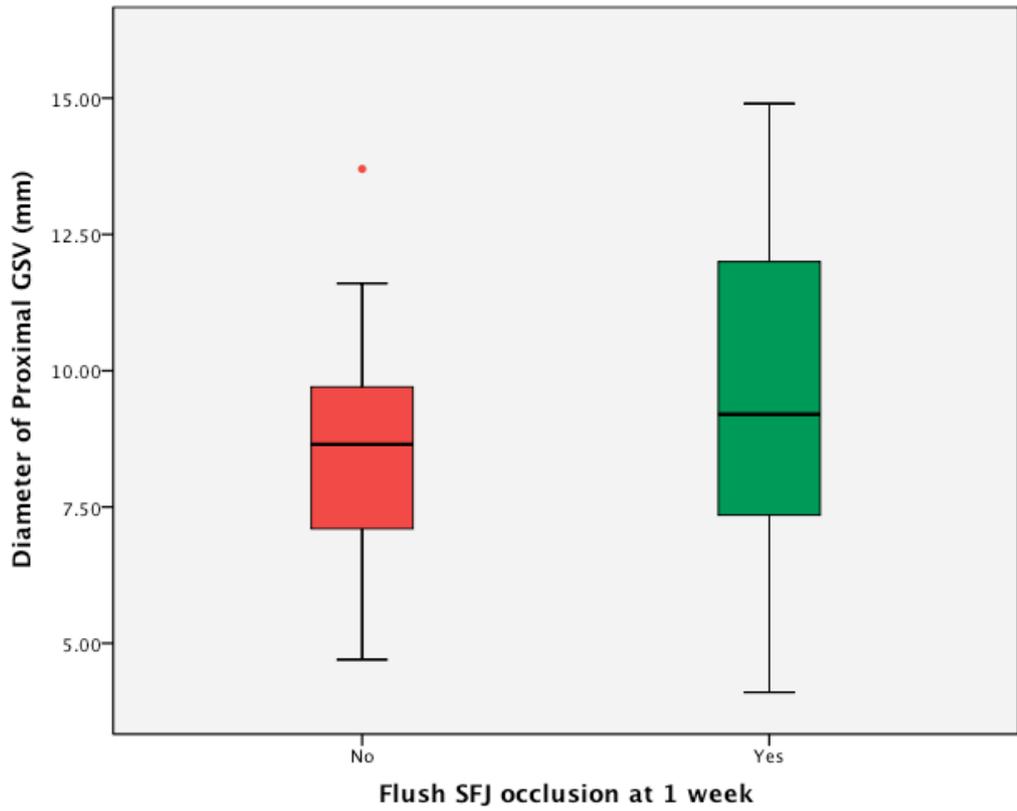
**Figure 41: Success of SFJ occlusion - Proximal GSV diameter (Study 3)**
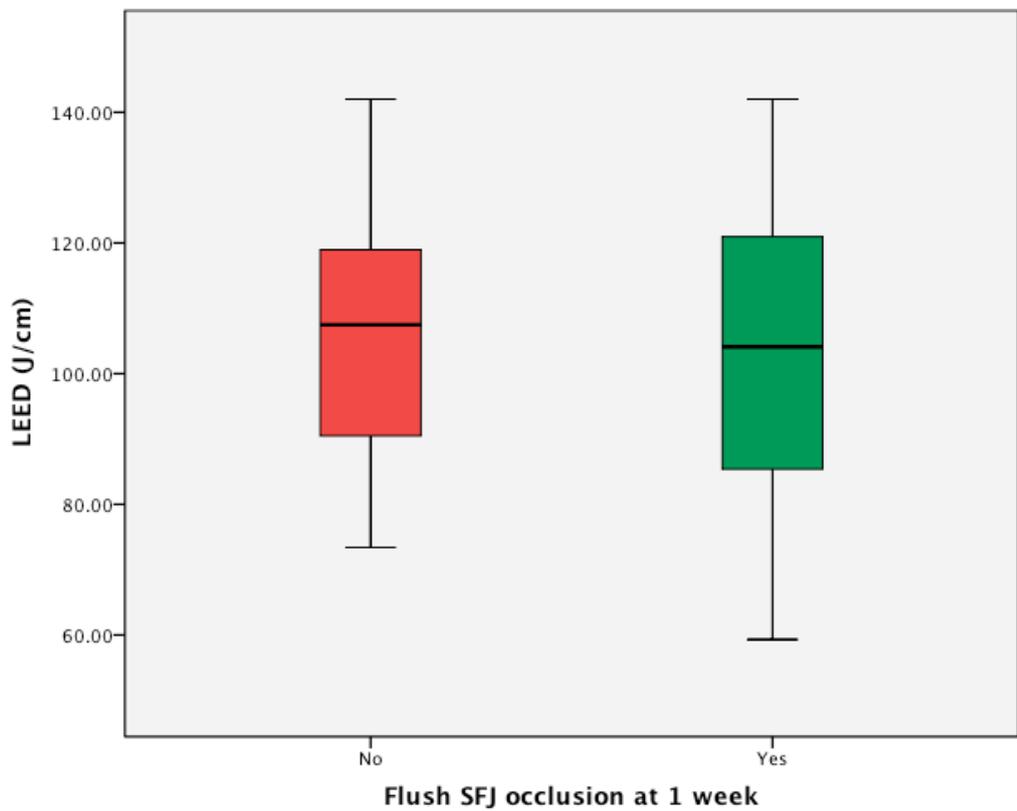


**Figure 42: Success of SFJ occlusion - LEED (Study 3)**

# 3.4 Study 4: Prospective cohort study of EVLA with either concomitant phlebectomy or foam sclerotherapy of varicosities

EVLA with concomitant AP or Foam was undertaken in 25 and 21 consecutive patients respectively; the groups were well matched at baseline for clinical (Table 21), QoL (Table 22) and DUS (Table 23) characteristics.

| Clinical Characteristics | | AP n=25 | Foam n=21 | p value |
|---|---|---|---|---|
| Age (years) | | 53 (25) | 56 (22) | 0.856 |
| Female sex | | 16/25 | 14/21 | 0.735 |
| Left leg | | 11/25 | 10/21 | 0.089 |
| BMI (kgm$^{-2}$) | | 26.87 (22.65-31.39) | 27.72 (23.32-32.65) | 0.794 |
| VCSS | | 4 (4-8) | 5 (3-8) | 0.824 |
| CEAP Clinical Grade | C2 | 16 | 13 | |
| | C3 | 2 | 2 | |
| | C4 | 6 | 5 | 0.512 |
| | C5 | 1 | 1 | |
| | C6 | 0 | 0 | |

**Table 21: Baseline Clinical Characteristics (Study 4)**

| QoL Characteristics | AP | Foam | p value |
|---|---|---|---|
| SF36 | | | |
| Physical Functioning | 85 (70-97.5) | 92.5 (76.25-100) | 0.387 |
| Role-physical | 100 (62.5-100) | 100 (93.75-100) | 0.748 |
| Bodily pain | 74 (51-84) | 78 (51.75-88) | 0.831 |
| General Health | 77 (53.5-87) | 77 (59-90.5) | 0.758 |
| Vitality | 70 (42.5-77.5) | 75 (50-85) | 0.128 |
| Social Functioning | 100 (62.5-100) | 100 (59.375-100) | 0.573 |
| Role-emotional | 100 (83.33-100) | 100 | 0.890 |
| Mental Health | 84 (66-92) | 88 (61-92) | 0.746 |
| EQ5D | 0.796 (0.743-0.924) | 0.796 (0.538-1.000) | 0.540 |
| AVVQ | 12.61 (10.23-16.24) | 16.01 (11.67-20.61) | 0.115 |

**Table 22: Baseline QoL Characteristics (Study 4)**

| DUS Characteristics | | AP | Foam | p value |
|---|---|---|---|---|
| SFJ Reflux | | 25/25 | 21/21 | 1.00 (FET) |
| GSV diameter | Prox | 8.2 (7.10-12.10) | 7.65 (5.3-13.83) | 0.797 |
| (mm) | Mid | 6.6 (5.80-7.70) | 6.45 (4.73-8.80) | 0.875 |

**Table 23: Baseline DUS Characteristics (Study 4)**

All patients attended their 1-week and 6-week appointments; 1 patient in each group failed to return at 12 weeks.

## Clinical Outcomes

### Periprocedural

All patients in the AP group underwent the planned procedure. The median (iqr) length of GSV treated with EVLA was 44.5cm (33.0-59.25) in the AP group and 51.0cm (42-62.5) in the Foam group (p=0.112, MWU). LEED was also similar at 87Jcm$^{-1}$ (79.0-97.0) and 100Jcm$^{-1}$ (75.7-104.95) for the AP and Foam groups respectively (p=0.276).

Three FS patients underwent EVLA alone due to difficult access of varicosities; two of these patients required subsequent AP for residual varicosities at 12 weeks. The third patient expressed an interest in further foam sclerotherapy, but declared they were shortly being admitted for an inpatient alcohol addiction rehabilitation programme, hence treatment was deferred and the patient was subsequently lost to follow-up. One patient in the AP group underwent further phlebectomy of a residual varicosity following 12-week review.

### Postprocedural

#### Pain

There were no differences in the pain scores between the two treatment groups at any time point over the first postoperative week (p=0.192-0.789, MWU, Figure 43), with a significant decrease in pain from the day of treatment to day 6 in both the AP (p<0.001, F-A) and Foam (p<0.001, F-A) groups.
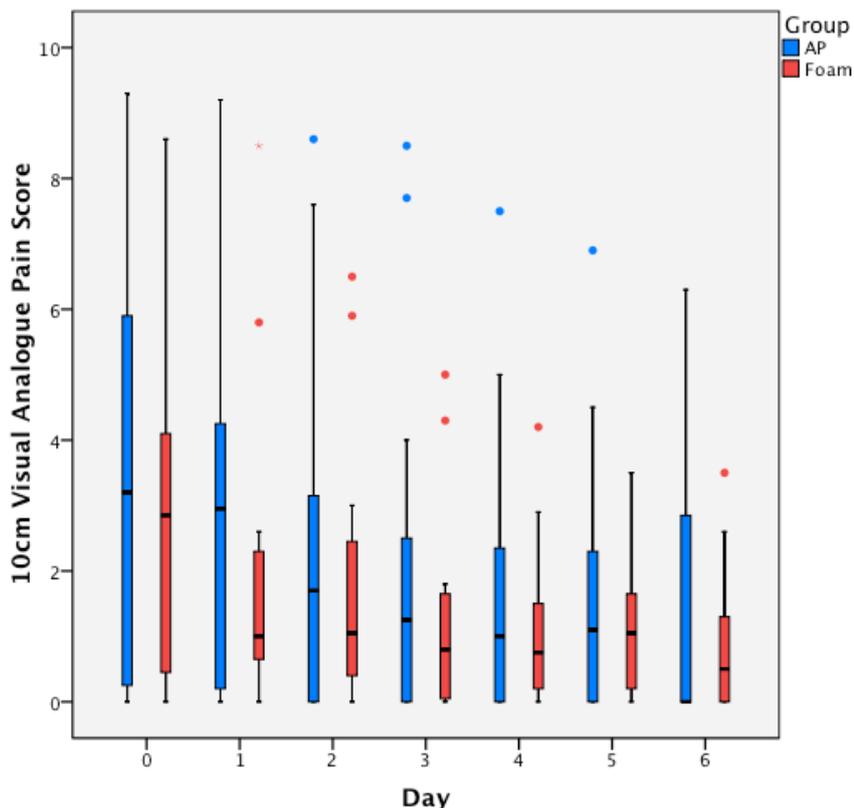
**Figure 43: Patient-reported post-procedural pain (Study 4)**

Complications

Overall complications were both relatively infrequent and minor in consequence (Table 24). There was a trend toward more superficial thrombophlebitis in the Foam group (p=0.08); all patients resolved by 12-week follow-up following treatment with diclofenac 50mg TDS and heparinoid 0.3% w/w cream (Hirudoid™, Genus Pharmaceuticals Ltd, Newbury, UK), topically QDS.

| Complication | AP | Foam | p value |
|---|---|---|---|
| Infection | 0 | 0 | N/A |
| VTE/eHIT | 0 | 0 | N/A |
| Superficial thrombophlebitis | 0 | 3 | 0.08 (FET) |
| Sensory disturbance | 1 | 1 | 1.00 (FET) |
| Skin staining | 2 | 5 | 0.220 (FET) |

**Table 24: Post-procedural complications (Study 4)**

Time to resume normal activities

As shown in Figure 44, there were no differences in median (iqr) time to resume normal activity; 1 day (1-5) in the AP group and 1 day (1-3) in the Foam group

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(p=0.129).   The outliers in the Foam group represent the patients with superficial thrombophlebitis.   The extreme outlier in the AP group (21 days) represents a professional driver who was signed off for three weeks by his employing company's occupational health department.
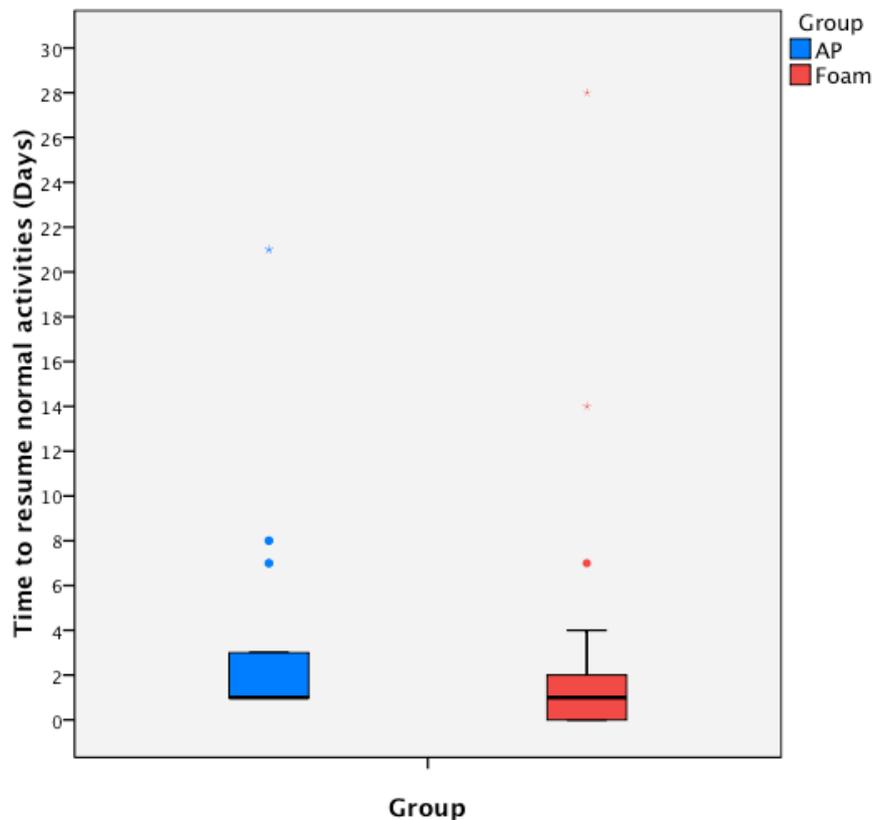


**Figure 44: Time to resume normal activities (Study 4)**

Patient Satisfaction

Patient satisfaction with the overall treatment at 12 weeks was high in both groups (Figure 45) with median (iqr) scores for satisfaction of 10 (9-10) and 10 (8.25-10) for AP and Foam respectively (p=0.653, MWU).   Satisfaction with cosmesis was also high, with similar scores for AP and Foam of 9 (8-10) and 9.5 (7.125-10) (p=0.814, MWU).
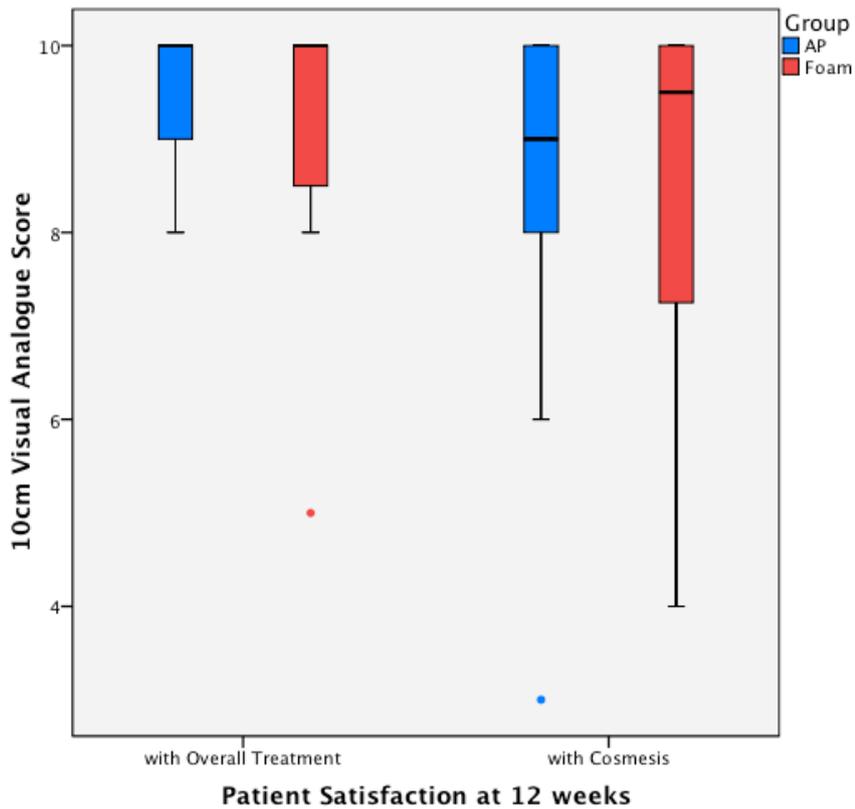
**Figure 45: 12-week Patient Satisfaction Scores (Study 4)**

VCSS

Notwithstanding the similar patient-reported scores above, objective clinical severity scoring with the VCSS revealed significantly better (lower) scores at 12 weeks for AP than Foam (median [iqr] 0 (0-0) versus 1 (0-2), $p=0.007$, Figure 46), although both groups significantly improved over baseline (AP, $p<0.001$; Foam, $p=0.002$, WSR)
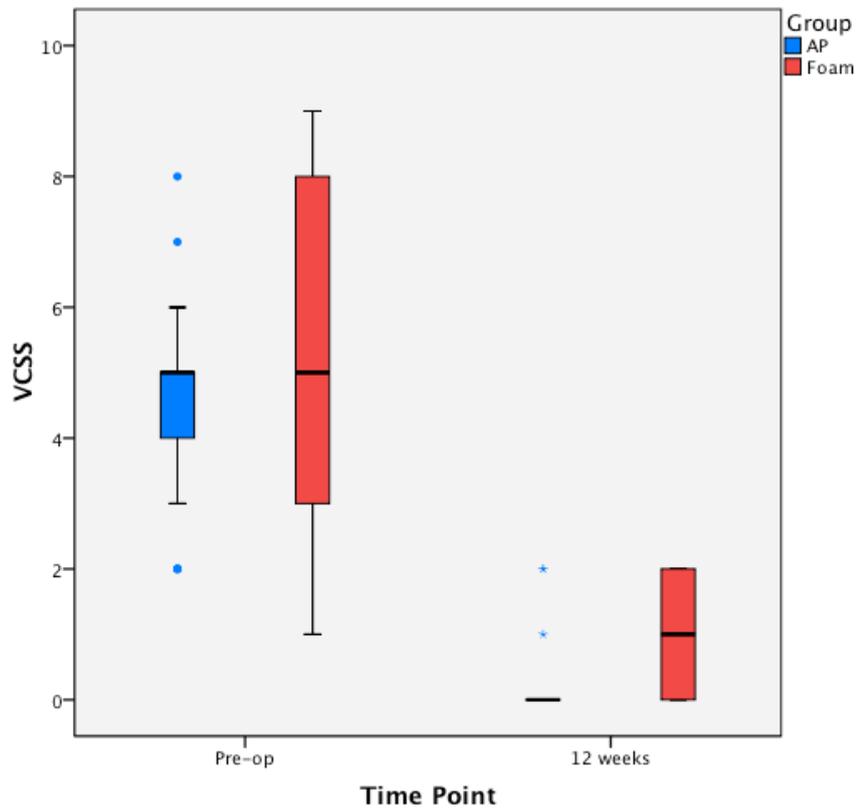
**Figure 46: VCSS at baseline and 12 weeks (Study 4)**

## QoL Outcomes

Figure S- 7, p.281, shows the SF36 domain scores over time by treatment group.

### SF36 Domains – Intergroup analysis, AP versus Foam

Intergroup comparisons showed no differences between any of the domain scores for the AP and Foam groups at any time point from baseline to 12 weeks (p=0.078-1.000, MWU).

### SF36 Domains – Intragroup analysis

#### AP

At 1 week, there were no differences from baseline for any of the SF36 domains (PF: p=0.809, R-P: p=0.180, BP: p=0.159, GH: p=0.163, Vit: p=0.454, SF: p=0.584, R-E: p=0.864, MH: p=0.583).

At 6 weeks, there were no differences over baseline in any of the domains (PF: p=0.754, R-P: p=0.720, BP: p=0.214, GH: p=0.585, Vit: p=0.110, SF: p=0.440, R-E: p=0.863, MH: p=0.434).

At 12 weeks, the AP group showed significant improvements over baseline scores for R-P (p=0.045), GH (p=0.005) and Vit (p=0.049). There were no changes over baseline in the other domain scores (PF: p=0.158, BP: p=0.089, SF: p=0.752, R-E: p=0.832, MH: p=0.265).

#### Foam

At 1 week, the Foam group displayed significant deterioration over baseline in the domain scores for PF (p=0.031) and BP (p=0.014). There were no differences over baseline in any of the other domain scores (R-P: p=0.334, GH: p=0.659, Vit: p=0.453, SF: p=0.56, R-E: p=0.891, MH: p=0.720).

There were no differences over baseline for any domain score at 6 weeks (PF: p=0.263, R-P: p=0.785, BP: p=0.482, GH: p=0.112, Vit: p=0.739, SF: p=1.000, R-E: p=0.785, MH: p=0.527), or at 12 weeks (PF: p=0.058, R-P: p=0.785, BP: p=0.161, GH: p=0.139, Vit: p=0.797, SF: p=0.932, R-E: p=0.705, MH: p=0.944)

### EQ5D Utility Index Scores

Figure 47 shows the changes in EQ5D score over time in each treatment group. On intergroup analysis, there were no differences between the groups at any time point from baseline to 12 weeks (p=0.540, 0.304, 0.575 and 0.312 respectively).

Intragroup analysis revealed no differences in the 1-week scores over baseline in the AP group (p=0.101), while there was a trend towards worse scores at 1 week in the Foam group (p=0.071). Median scores in the AP group improved significantly over baseline at 6 (p=0.004) and 12 weeks (p=0.012). However, there were no significant improvements over baseline in the foam group at either 6 weeks (p=0.225) or 12 weeks (p=0.399).
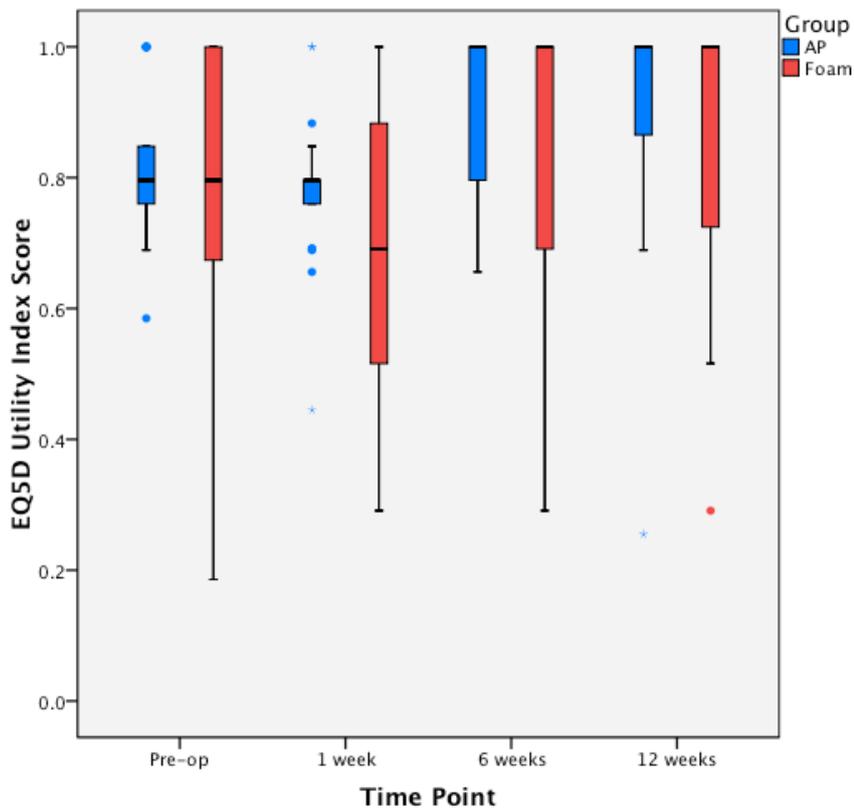


**Figure 47: EQ5D Utility Index Scores over time (Study 4)**
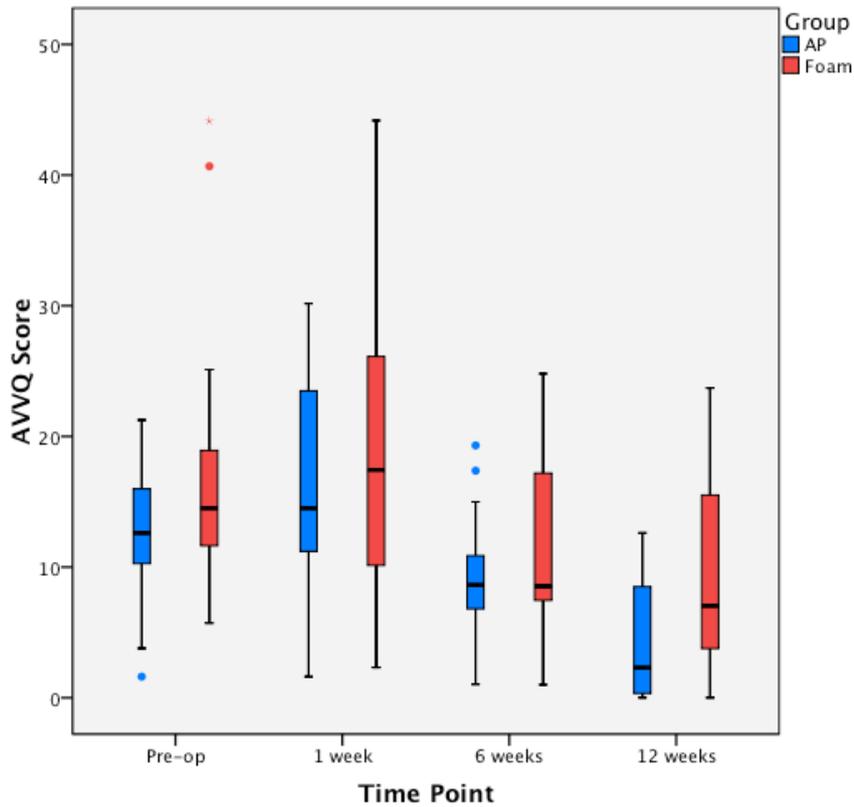
**Figure 48: AVVQ Scores over time (Study 4)**

Figure 48 shows the AVVQ scores for both treatment groups over time. Intergroup analysis showed a significantly lower (better) score in the AP group over the Foam group at 12 weeks (p=0.037). There were no differences between the groups at any other time point.

On intragroup analysis, the AP group had significantly worse scores over baseline values at 1 week (p=0.033). At 6 weeks and 12 weeks, the AVVQ scores were significantly improved over baseline (p=0.019 and <0.001 respectively). On intragroup analysis in the Foam group, 1-week scores were no different to baseline values (p=0.227). 6 week and 12 week scores were significantly improved over baseline (p=0.007 and 0.013 respectively).

## DUS Outcomes

DUS-determined GSV closure rates were 100% in both groups at 1 and 12 weeks, with no evidence of flow in the treated length of GSV for any patient. A flush SFJ occlusion was aimed for in all patients, but only achieved in 12 of 25 and 10 of 21 patients in the AP and Foam groups respectively (p=0.363, $\chi^2$) at 1 week. At 1 week in the patients with a patent SFJ, 3 of 13 were incompetent in the AP group, while none of 11 was incompetent in the Foam group (p=0.268, FET). By 12 weeks, 1 of the 3 incompetent SFJs in the AP group had become competent; at 12 weeks there were 2 incompetent SFJs in the AP group and 1 in the Foam group (p=1.000, FET). No successfully occluded SFJ at 1 week became patent at 12 weeks.

Analysing patients with successful SFJ closure versus those without, there were no differences in either proximal GSV diameters (median [iqr]: 8.1mm [5.1-11.6] versus 7.2mm [6.3-12.7], p=0.882, MWU, Figure 49), or LEED administered (median [iqr]: 89.0 Jcm$^{-1}$ [79.0-105.8] versus 87 Jcm$^{-1}$ [81.6-100.0], p=0.935, MWU; Figure 50); both factors that could conceivably have made a difference to success.
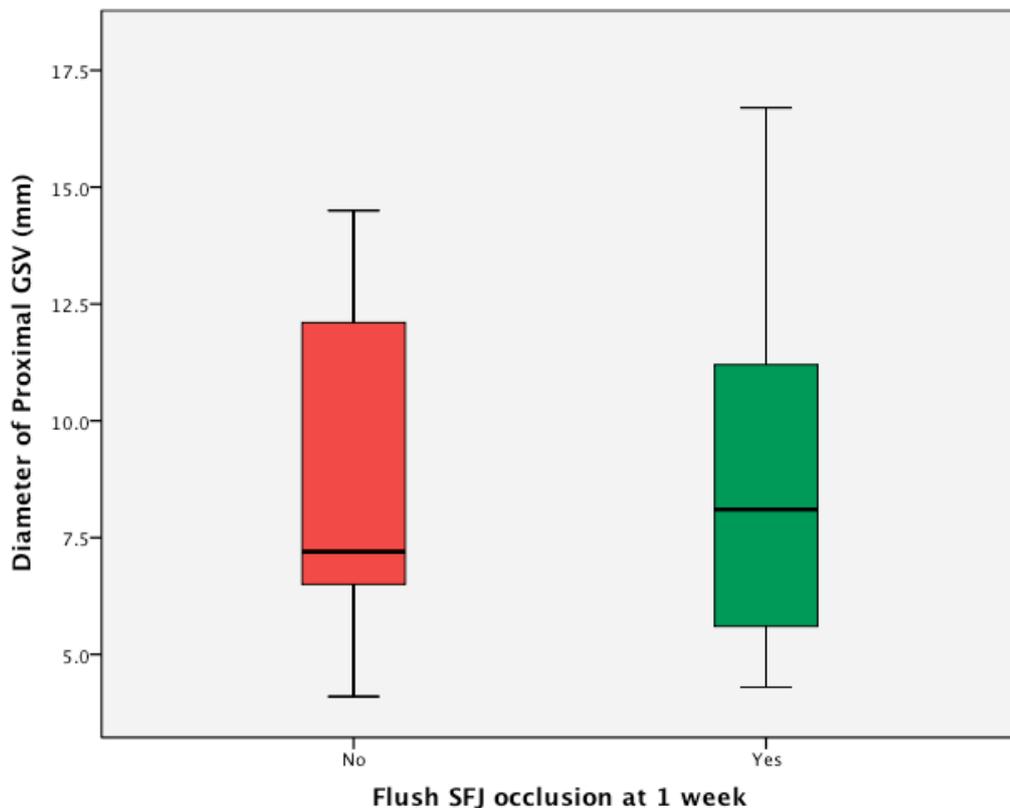


**Figure 49: Success of flush SFJ occlusion – Baseline Proximal GSV diameter (Study 4)**
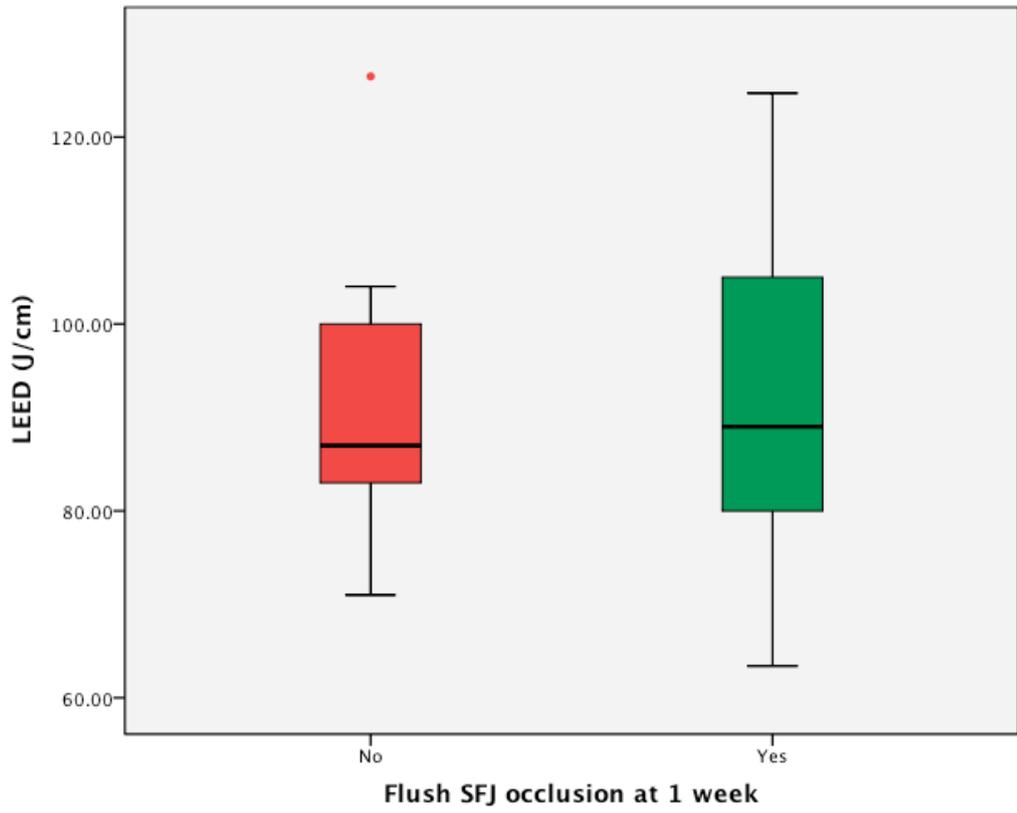
**Figure 50: Success of flush SFJ occlusion – LEED administered (Study 4)**

## 3.5 Study 5: Prospective cohort study of 810nm versus 1470nm EVLA

25 consecutive patients with primary, unilateral, symptomatic SVI attributable to SFJ/GSV reflux underwent EVLA (810nm, 14W continuous mode) with AP by the same investigator. A subsequent 25 consecutive patients with the same disease pattern underwent EVLA (1470nm, 8W continuous mode) with AP, also by the same investigator.

Baseline clinical, QoL and DUS characteristics were not significantly different between the groups (Table 25, Table 26, Table 27).

| Clinical Characteristics | | 810nm | 1470nm | p value |
|---|---|---|---|---|
| Age (years) | | 55 (25) | 48 (22) | 0.204 |
| Female sex | | 16/25 | 18/25 | 0.762 |
| Left leg | | 10/25 | 16/25 | 0.089 |
| BMI (kgm$^{-2}$) | | 28.1 (5.74) | 28.8 (10.95) | 0.478 |
| VCSS | | 6 (4-8) | 5 (4-8) | 0.390 |
| CEAP Clinical Grade | C2 | 13 | 17 | 0.201 |
| | C3 | 3 | 5 | |
| | C4 | 7 | 3 | |
| | C5 | 2 | 0 | |
| | C6 | 0 | 0 | |

**Table 25: Baseline Clinical Characteristics (Study 5)**

| QoL Characteristics | 810nm | 1470nm | p value |
|---|---|---|---|
| SF36 | | | |
| Physical Functioning | 90 (30) | 90 (20) | 0.952 |
| Role-physical | 100 (38) | 100 (0) | 0.404 |
| Bodily pain | 74 (32) | 72 (33) | 0.845 |
| General Health | 77 (37) | 77 (30) | 0.984 |
| Vitality | 70 (33) | 75 (25) | 0.578 |
| Social Functioning | 100 (25) | 100 (18.8) | 0.579 |
| Role-emotional | 100 (0) | 100 (0) | 0.253 |
| Mental Health | 88 (28) | 92 (20) | 0.180 |
| EQ5D | 0.796 (0.240) | 0.796 (0.105) | 0.123 |
| AVVQ | 15.01 (7.933) | 14.55 (8.070) | 0.404 |

**Table 26: Baseline QoL Characteristics (Study 5)**

| DUS Characteristics | | 810nm | 1470nm | p value |
|---|---|---|---|---|
| SFJ Reflux | | 25/25 | 24/25 | 1.00 (FET) |
| GSV diameter | Prox | 10.2 (8.35-13.05) | 8.15 (5.15-12.85) | 0.074 |
| (mm) | Mid | 6.6 (4.95-11.05) | 5.4 (3.9-7.88) | 0.341 |

**Table 27: Baseline DUS Characteristics (Study 5)**

There was minimal loss to follow-up; all patients attended their 1-week appointment, 1 patient in each group failed to return at 6 and 12 weeks, with a further 1 patient failing to attend at 12 weeks in the 1470nm group.

## Clinical Outcomes

### *Periprocedural*

All 25 patients in each group underwent the planned intervention as a "walk-in, walk-out" daycase procedure with no peri-procedural problems or adverse events.

The median (iqr) length of vein treated was similar between the 810nm and 1470nm groups at 51cm (922.0) and 53.5cm (23.88) respectively (p=0.510, MWU). Similarly, there was no difference in the volume of tumescent anaesthesia infused (600ml [237.5] versus 620ml [247.5], p=0.364, MWU) (Figure 51).
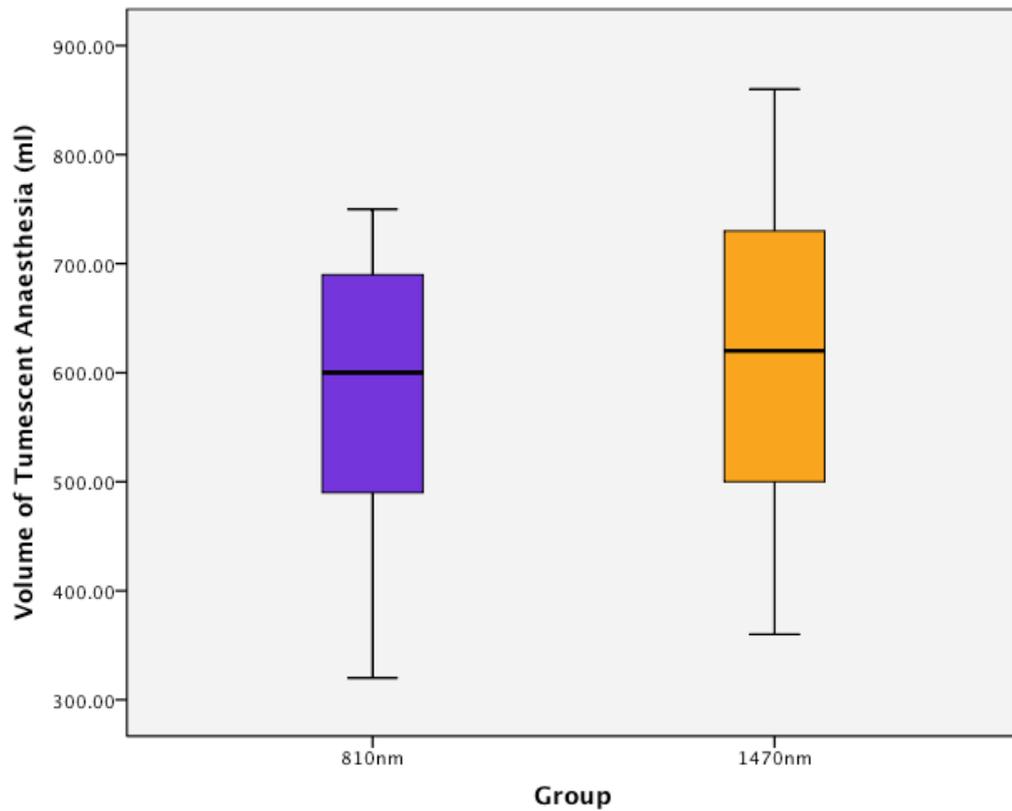
**Figure 51: Volume of tumescent anaesthesia infused (Study 5)**

Mean (SD) LEED was significantly lower in the 1470nm recipients, at 54 Jcm$^{-1}$ (13.38) compared to those receiving 810nm (104.5 Jcm$^{-1}$ [26.59], p<0.001, independent samples t-test).

*Postprocedural*

Pain

The 1470nm group reported significantly lower post-procedural pain scores, as assessed by patient-reported 10cm VAS, at all time points over the first week (Figure 52).
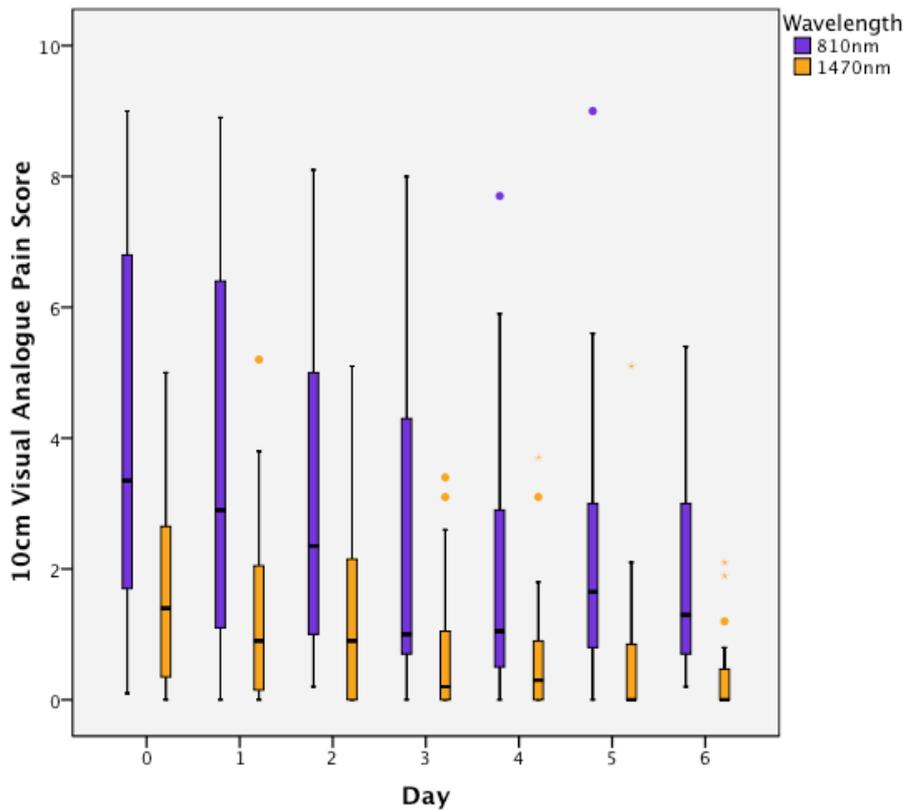
**Figure 52: Patient-reported post-procedural pain (Study 5)**

To further investigate the robustness of this finding, ROC Curves with AUC values were calculated. AUC values ranged between 0.756 and 0.879, significant at $p<0.05$ at each time point (Figure 53), indicating that there was at least a moderate-to-good predictive value of lower pain scores denoting treatment with 1470nm laser.
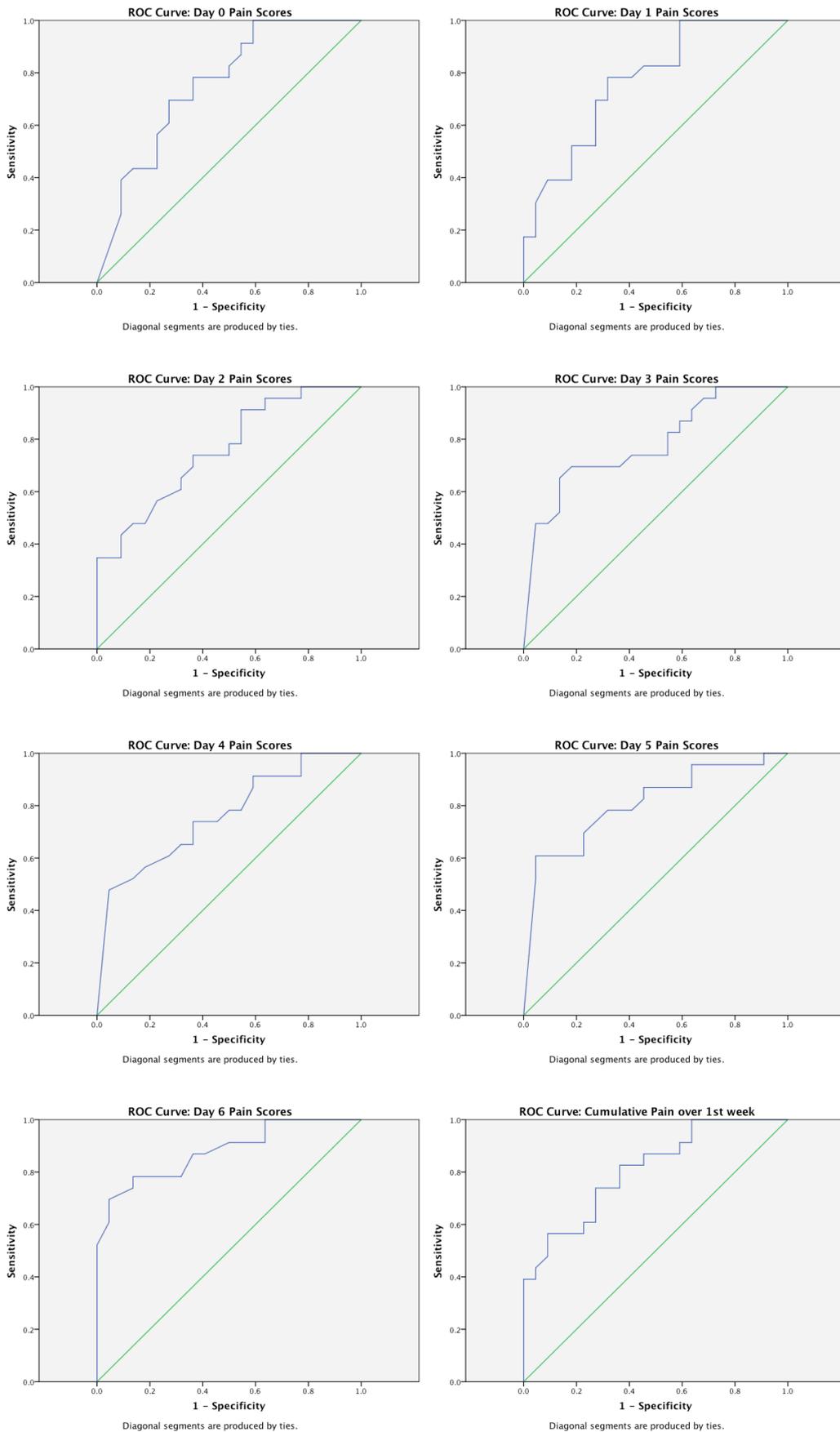
**Figure 53: ROC curves for patient-reported post-procedural pain (Study 5)**

AUC (95% CI), p value: Day 0: 0.768 (0.630-0.905), p=0.002; Day 1: 0.756 (0.614-0.898), p=0.003; Day 2: 0.759 (0.621-0.897), p=0.003; Day 3: 0.782 (0.647-0.916), p=0.001; Day 4: 0.761 (0.622-0.900), p=0.003; Day 5: 0.807 (0.678-0.936), p<0.001; Day 6: 0.879 (0.781-0.978), p<0.001; Cumulative pain: 0.809 (0.686-0.932), p<0.001.

This lower post-procedural pain with the 1470nm laser also translated into lower analgesia requirements on days 2 to 6 (Table 28, Figure 54).

| | 810nm | 1470nm | p value |
|---|---|---|---|
| Day 0 | 21 | 19 | 0.294 |
| Day 1 | 20 | 15 | 0.062 |
| Day 2 | 20 | 12 | 0.007 |
| Day 3 | 19 | 9 | 0.002 |
| Day 4 | 19 | 10 | 0.004 |
| Day 5 | 19 | 9 | 0.004 |
| Day 6 | 19 | 5 | <0.001 |

**Table 28: Post-procedural Analgesic requirements (Study 5)**

n=number of patients taking analgesia
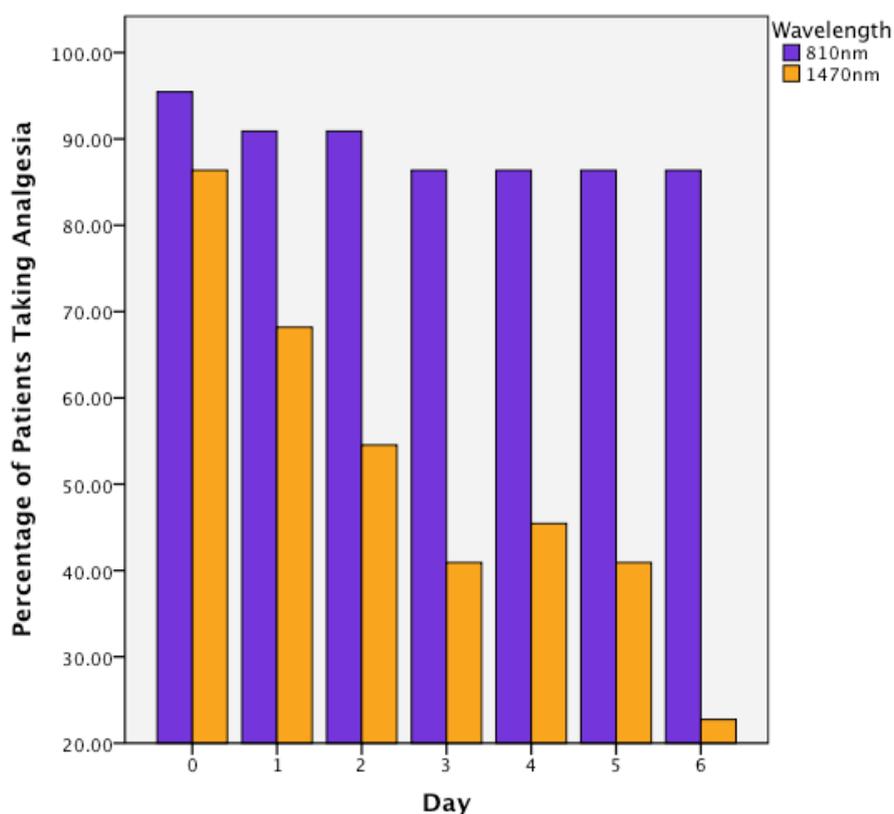


**Figure 54: Proportion of patients taking analgesia (Study 5)**

Complications

There were no peri-procedural complications. Post-procedural complications were few in both groups, with no significant events such as VTE or eHIT. There were no significant differences between the groups when assessing the individual

complications encountered, but overall complications were significantly more common in the 810nm group (Table 29)

| Complication | 810nm | 1470nm | p value |
|---|---|---|---|
| Infection | 0 | 0 | N/A |
| VTE/eHIT | 0 | 0 | N/A |
| Thrombophlebitis | 2 | 0 | 0.497 |
| Sensory disturbance | 4 | 0 | 0.120 |
| Skin staining | 1 | 0 | 0.289 |
| **Overall Complications** | 7 | 0 | 0.022 |

**Table 29: Post-procedural complications (Study 5)**

One patient in each group had limited, but symptomatic, residual varicosities at 12 weeks; both subsequently underwent further ambulatory phlebectomy without complication. A further patient in the 810nm group had a single residual varicosity that was asymptomatic and opted for conservative management.

### Time to resume normal activities

The differences in pain and complications did not translate into a difference between the groups in time to resume normal activities, with a median (iqr) of 1 (0-2) and 1 (1-2) days for 810nm and 1470nm respectively, p=0.318, MWU, Figure 55).
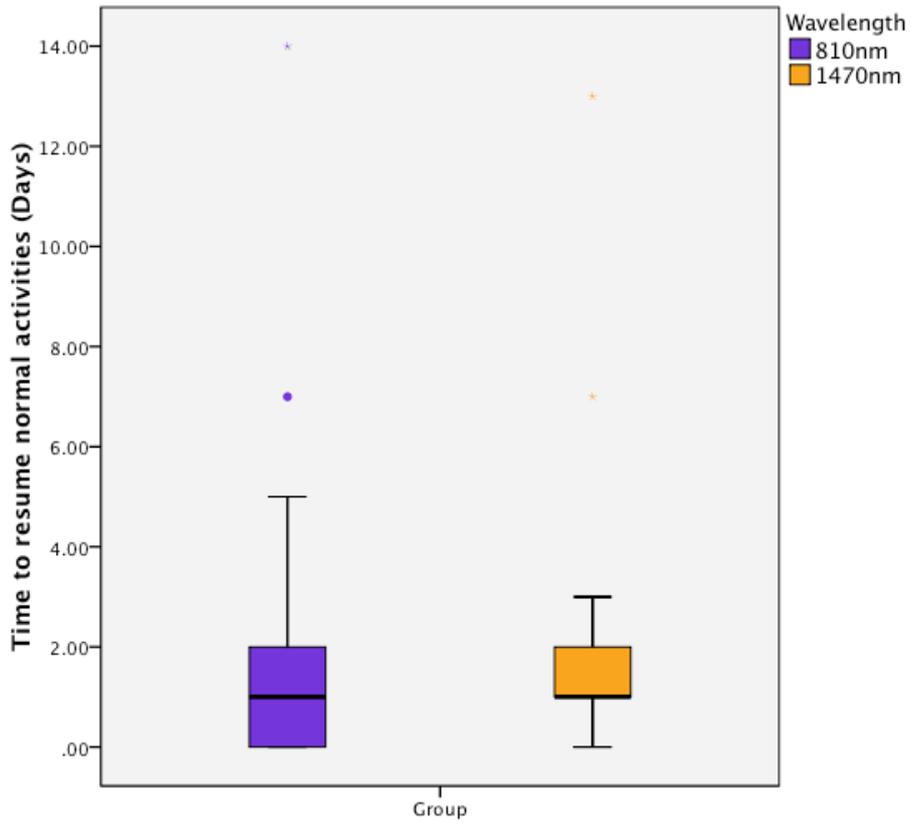
**Figure 55: Time to resume normal activities (days) (Study 5)**

## Patient Satisfaction

Patient satisfaction with both the overall treatment and cosmesis at 12-week follow-up was equally high in both wavelength groups, as shown in Figure 56.
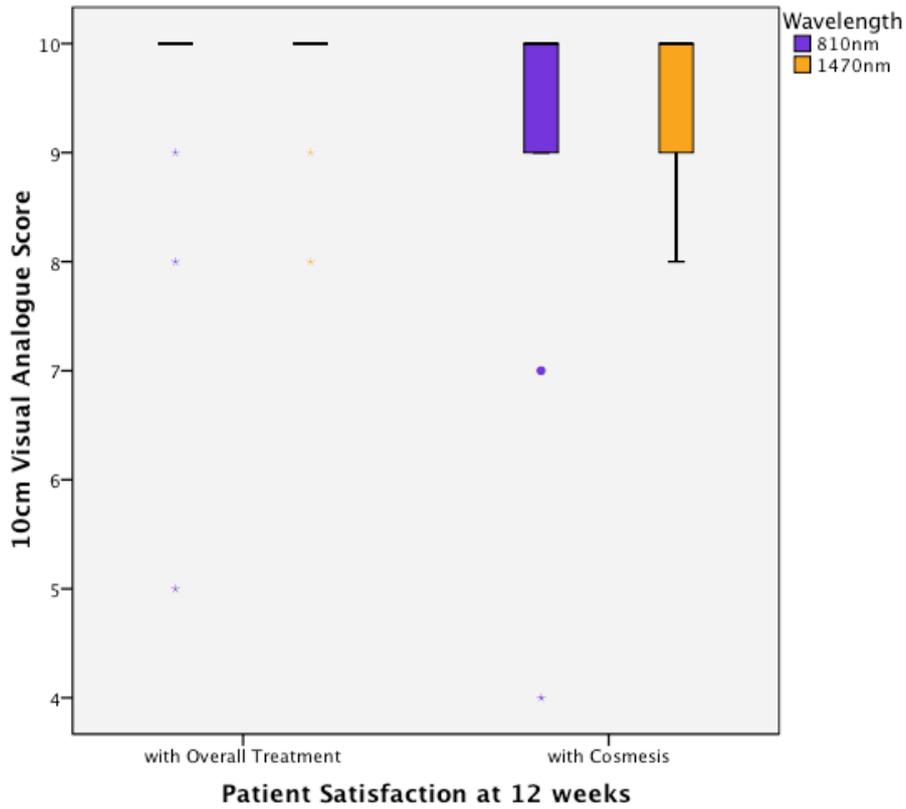
**Figure 56: 12-week Patient Satisfaction VAS (Study 5)**

VCSS

There were no intergroup differences between 810nm and 1470nm at 12 weeks (median [iqr] 1 [0-2] versus 0 [0-1] respectively), with both groups demonstrating significant ($p<0.001$, WSR) improvements over baseline values (Figure 57).
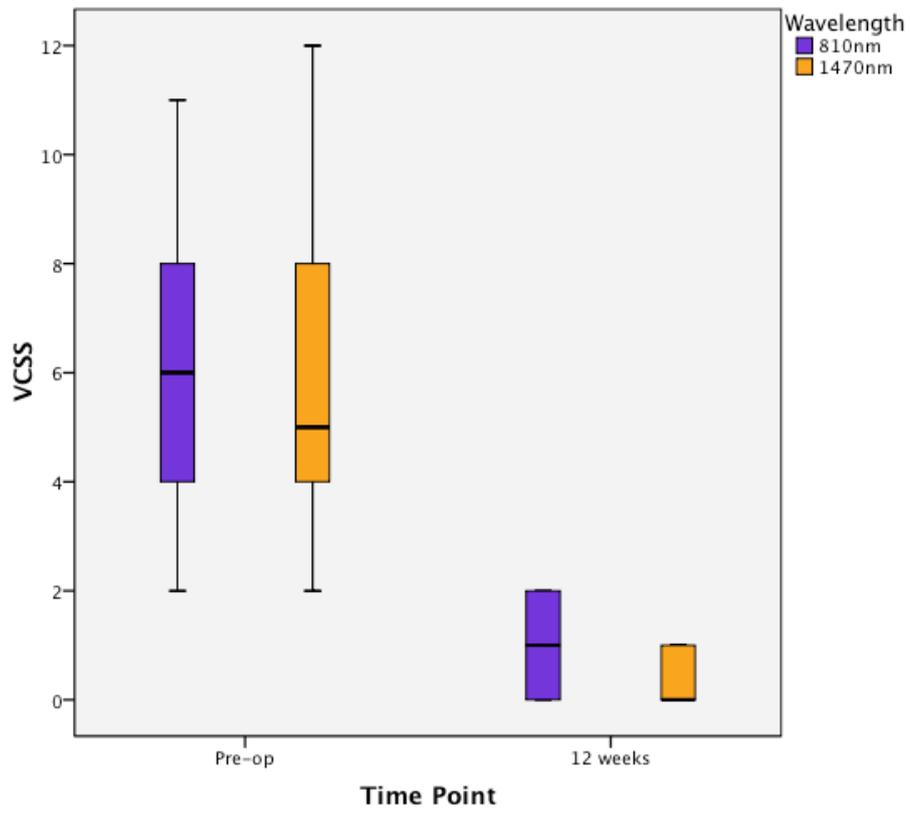
**Figure 57: VCSS over time (Study 5)**

## QoL Outcomes

Figure S- 8, p.284, displays the SF36 domain scores for the 810nm and 1470nm groups from baseline to 12-week follow-up.

*SF36 Domains – Intergroup analysis, 810nm versus 1470nm*

On intergroup analysis, the 1470nm group had significantly better Role-physical domain scores at 1 week (p=0.046, MWU) in comparison to the 810nm group, but there were no other differences between the two wavelengths at any time-point for any domain score; 1 week (PF p=0.449, BP p=0.132, GH p=0.766, Vit p=0.366, SF p=0.166, R-E p=0.256, MH p=0.216); 6 weeks (PF p=0.505, R-P p=0.200, BP p=0.439, GH p=0.577, Vit p=0.272, SF p=0.249, R-E p=0.135, MH p=0.731); 12 weeks (PF p=0.134, R-P p=0.508, BP p=0.605, GH p=0.495, Vit p=0.532, SF p=0.777, R-E p=0.610, MH p=0.078).

810nm

Intragroup analysis (WSR test) in the 810nm group identified significant deterioration in the domains of Physical Functioning (p=0.047), Role-physical (p=0.040), Bodily pain (p=0.001) and Social Functioning (p=0.024) from baseline to 1 week. There were no differences between baseline and 1 week in the domain scores for General Health (p=0.948), Vitality (p=0.112), Role-emotional (p=0.590) or Mental Health (p=0.418).

At 6 weeks, there were no differences from baseline for any of the SF36 domains (PF p=0.344; R-P p=0.339; BP p=0.753; GH p=0.396; Vit p=0.689; SF p=0.832; R-E p=0.892; MH p=0.595)

At 12 weeks, the 810nm group had significantly improved SF36 domain scores for Bodily pain (p=0.016) and General Health (p=0.0440). There were no differences over baseline scores for the other domains (PF p=0.161; R-P p=0.670; Vit p=0.236; SF p=0.071; R-E p=0.180; MH p=0.874).

1470nm

Compared to baseline scores, there were no changes to the SF36 domain scores at 1 week (PF p=0.260; R-P p=0.799; BP p=0.288; GH p=0.285; Vit p=0.586; SF p=0.141; R-E p=0.590; MH p=0.418).

At 6 weeks, there were significant improvements over baseline for domain scores in R-P (p=0.043), GH (p=0.027) and SF (p=0.026). The improvements in scores for PF (p=0.067), BP (p=0.051) and Vit (p=0.054) approached statistical significance. There were no differences over baseline in the 6-week scores for R-E (p=0.564) or MH (p=0.397).

There were sustained improvements over baseline in the 12-weeks scores for PF (p=0.035), BP (p=0.019), GH (0.016) and Vit (p=0.015). The domain scores for R-P (p=0.194), SF (p=0.168), R-E (p=0.168) and MH (p=0.236) were no different to baseline.

*EQ5D Utility Index Scores*

Figure 58 shows the EQ5D utility index scores for both groups at each time-point. On intergroup analysis, there were no differences between the wavelengths at any time-point (1 week p=0.250; 6 weeks p=0.191; 12 weeks p=0.246)

Intragroup analysis of the 810nm wavelength demonstrated significant worsening over baseline at 1-week follow-up (p=0.003). There was no such change in the 1470nm group (p=0.868). At 6 weeks, the 810nm group had equivalent EQ5D scores to baseline (p=0.513), while the 1470nm group had improved over baseline (p=0.026). At 12 weeks, both groups demonstrated significant improvements in EQ5D scores over baseline (810nm p=0.049; 1470nm p<0.001).
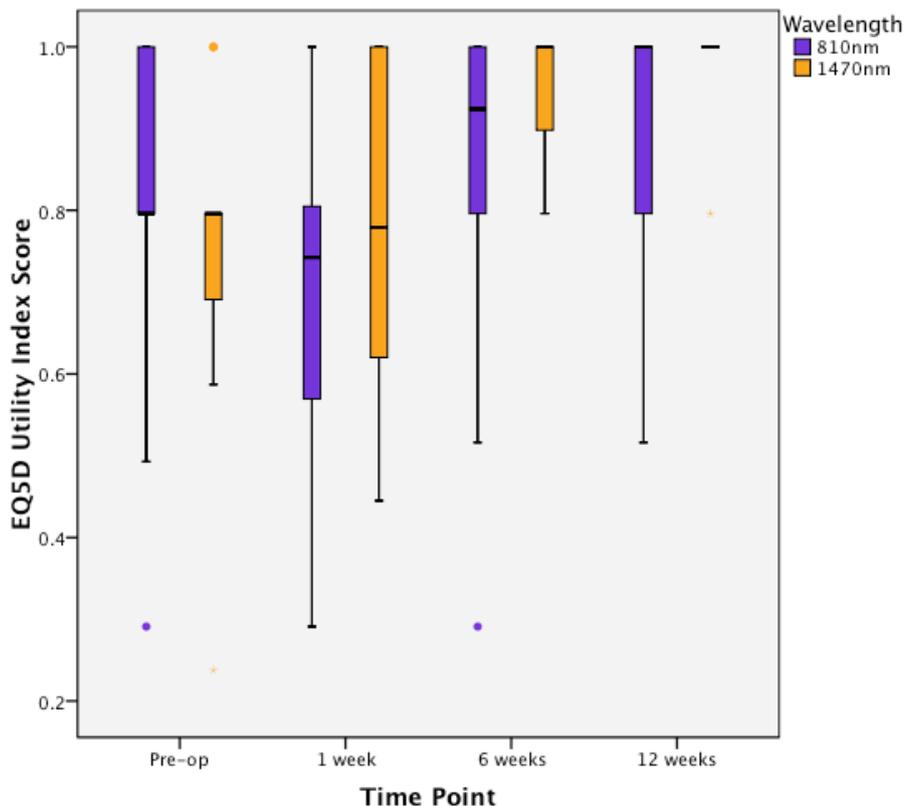


**Figure 58: EQ5D Utility Index Scores over time (Study 5)**

*AVVQ*

Figure 59 displays the AVVQ scores for both wavelength groups from baseline through to 12 weeks. Intergroup analysis found no significant difference between the groups at any time-point (1 week p=0.086; 6 weeks p=0.357; 12 weeks p=0.405).

Intragroup analyses showed no differences between baseline and 1-week AVVQ scores for either 810nm (p=0.278) or 1470nm (p=0.335).  At 6 weeks (p=0.004 and 0.001) and 12 weeks (p=0.001 and <0.001), there were significant improvements over baseline in the 810nm and 1470nm groups respectively.
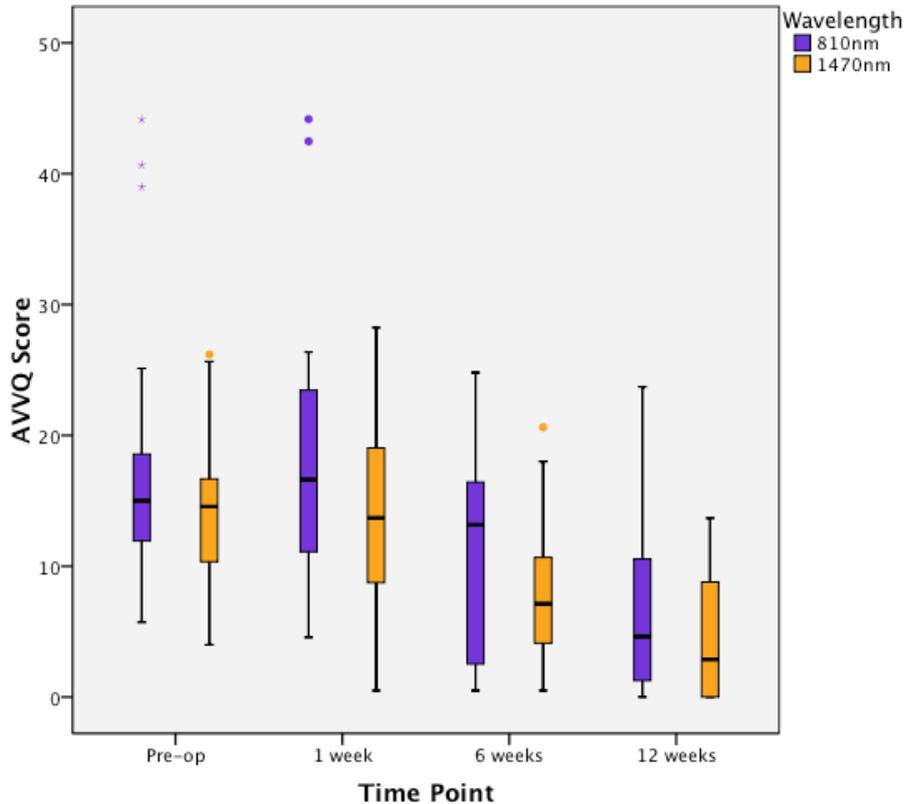


**Figure 59: AVVQ scores over time (Study 5)**

## DUS Outcomes

All patients were adjudged to have received a technically successful ablation, with no residual reflux at the SFJ or flow in the treated GSV at any time-points from 1 to 12 week follow-up.  Despite aiming for a flush SFJ occlusion, this was only achieved in 14 patients in each group at 1 week DUS assessment.  By 12 weeks, this had fallen to 11 patients in each group.

Both groups demonstrated significant GSV shrinkage over time (p<0.001 for both 810nm and 1470nm groups, F-A), with no significant differences in vein diameters between the two wavelengths at any point (p=0.060-0.745, MWU) (Figure 60 and Figure 61).
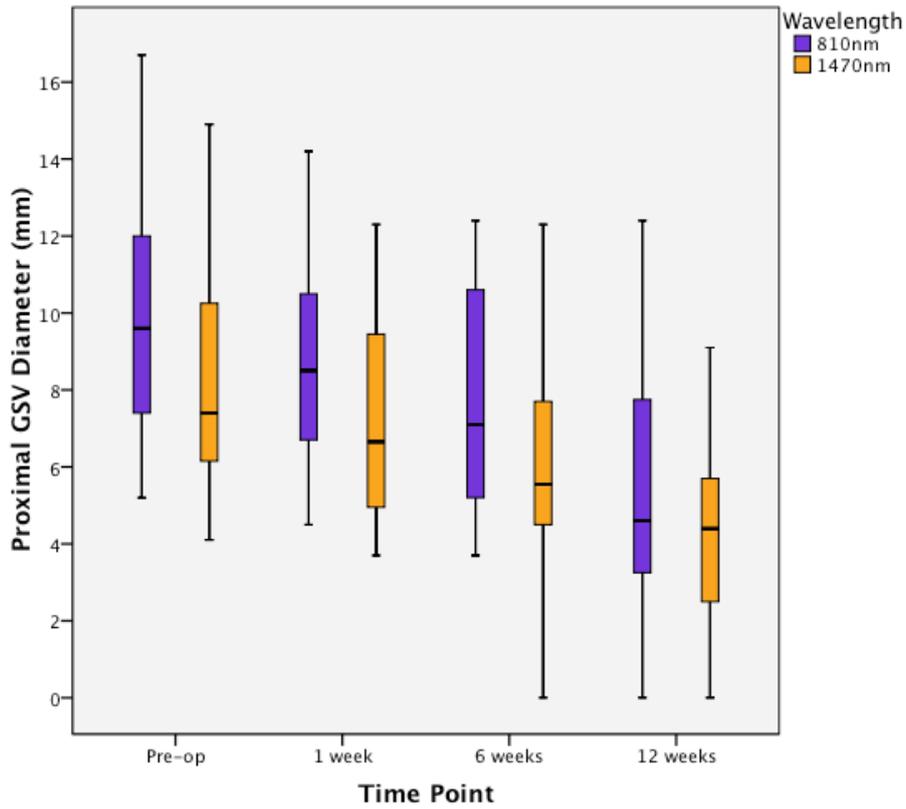
**Figure 60: Proximal GSV diameters over time (Study 5)**
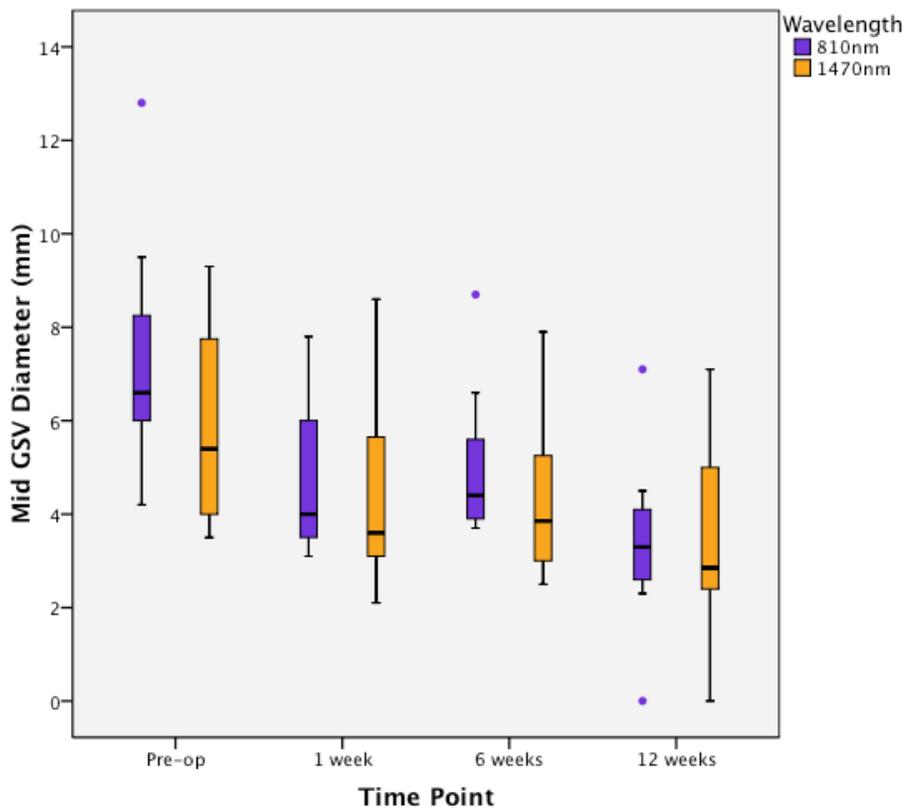


**Figure 61: Mid GSV diameters over time (Study 5)**

# Chapter 4: Discussion

The HELP-1 RCT clearly demonstrates the short-term benefits, up to one year[378], of EVLA over Surgery for treatment of primary, symptomatic GSV insufficiency. In comparison with surgery, patients receiving EVLA report less postoperative pain, with a quicker return to full activity and employment, and a relatively preserved short-term QoL. Clinical recurrence rates at one year following EVLA are significantly lower than after Surgery.

The two-year results of the HELP-1 RCT reported in Study 1 show a continued significant benefit of EVLA over Surgery in terms of lower clinical recurrence rates. Patient satisfaction remained high, while improvements in VCSS were maintained in both groups. Improved generic and disease-specific QoL is maintained in both treatment groups over baseline values, with no intergroup differences.

Overall, follow-up attendance rates were good, and similar or superior to other studies of SVI, both in the short-[358,359,364] and medium-term[417,418]. Where patients did not attend scheduled two-year follow-up in Study 1, attempts were made at telephone contact. Of those successfully contacted, no patient stated any concerns with recurrent varicosities, symptoms or dissatisfaction with their treatment outcome. It would therefore seem reasonable to surmise that the clinical data observed in this study is a true representation of real-life outcomes and that the chance of significantly different findings if all patients attended follow-up is unlikely.

In summary, Study 1 demonstrates that EVLA provides at least equivalent outcomes to the traditional gold-standard of conventional surgery in the medium term (2 years) following treatment for symptomatic GSV insufficiency. Studies 3 - 5 suggest there is the potential for technical modifications of the EVLA procedure which may improve both the short-term patient experience and long-term clinical, QoL and DUS outcomes.

## Clinical Recurrence

The 2-year findings from the HELP-1 RCT in Study 1 show that EVLA results in significantly lower clinical recurrence compared with Surgery. The data presented provide valuable evidence of the pathogenesis and patterns of clinical recurrence after conventional surgery and EVLA, as well as their impact on objective clinical severity scoring and QoL. Rasmussen *et al* claimed that the recurrent varicose veins seen at 1-year follow up in their RCT of ClosureFast, EVLA, UGFS and Surgery had minor clinical relevance[417], however, they did not undertake comparisons of clinical and QoL outcomes of those with and without clinical recurrence and hence that statement is unsubstantiated.

In Study 1, no presumptions of clinical relevance were made; clinical recurrence was defined in keeping with the REVAS consensus[419], assessed and analysed regardless of any patient-reported symptoms. The data clearly demonstrate that recurrent varicosities are clinically relevant, resulting in higher VCSS, impaired disease-specific Qol and lower patient satisfaction when compared with patients who have freedom from recurrence. This is in keeping with a previous report that patients' fear of recurrence is very high[383]. It is therefore important to identify technical factors that could reduce recurrence. Furthermore, the sub-group analysis of Surgery versus EVLA for patients demonstrating clinical recurrence suggests that the QoL response to recurrence may be different between the treatment modalities.

Freedom from clinical recurrence was reported using the Kaplan-Meier survival method, which has long been used in the arterial and cancer literature, and will allow for transparent reporting of clinical success over time in long-term follow-up[146].

### *Surgery*

Clinical recurrence of varicose veins after surgery has historically been attributed to technical or tactical error[420], although neovascularization has ultimately proved to be responsible for the majority of recurrences in technically and tactically correct surgery[184,419], in combination with disease progression from previously untreated sources.

Previous debate centred on whether groin recurrence is due to true neovascularization or simply the dilatation of existing collaterals. DUS findings from Study 1, combined with other DUS, clinical and histological reports[419,421-425] should conclusively end this debate, certainly in the context of technically correct primary surgery; the majority of clinical recurrence in the groin following conventional surgery is due to neovascularization secondary to surgical trauma.

Recurrence in the Surgery group in Study 1 was shown to occur despite technically correct surgery confirmed on postoperative DUS. The majority of recurrences in this group arose from either groin neovascularization or residual below-knee GSV incompetence, as demonstrated by the ORs of 2.96 and 3.66 respectively.

In Study 1, rates of recurrent veins attributable to technical or tactical error are significantly lower than those reported in the REVAS study[419], whilst the observed rate of neovascularization was higher than that reported by the REVAS authors, but in keeping with data from other studies of EVTA versus surgery[426,427]. This may be explained by the fact that all patients in Study 1 underwent thorough preoperative DUS, thus allowing accurate operative planning; technically correct surgery was further confirmed postoperatively in all patients. The merits of preoperative DUS in reducing recurrence following conventional surgery have been proven by RCT evidence[184].

The results of Surgery in Study 1 are similar to those reported by Jones *et al*[58], where stripping the GSV reduced clinical recurrence at 2 years from 43% to 25%. DUS-detected neovascularisation at 1 year has been shown to be a strong predictor for future clinical recurrence[268]. This reflects the likelihood that clinically obvious recurrence secondary to neovascularization has a certain lead-time, particularly in patients in whom the GSV has been adequately stripped. The 10% of Surgery patients in Study 1 in whom neovascularization was noted, but did not display clinical recurrence, is a concern; these patients may subsequently return with clinical recurrence in the future.

As demonstrated by the REVAS study, clinical recurrence of varicosities after surgery in Study 1 was commonly related to either groin neovascularization or below-knee GSV disease, with more than one source often being identified[419]. These patterns of clinical recurrence after surgery are related to technical aspects that cannot be easily addressed or improved upon; as discussed earlier, neovascularization has been

notoriously difficult to prevent, while stripping of the below-knee GSV significantly increases complication rates[258].


## *EVLA*

In the EVLA group, DUS revealed areas where modification to the technique may further reduce recurrences.


### Importance of a Flush SFJ occlusion

10 of the 16 recurrences in the EVLA group of Study 1 were related to an incompetent SFJ with reflux into proximal GSV tributaries (typically the AASV). The data from Study 1 demonstrate that all patients received sufficient energy to give a successful, durable closure of the GSV trunk. However, in patients with recurrence of above-knee disease attributable to patent groin tributaries, all were associated with an incompetent SFJ; these patients received a significantly lower LEED than patients without this pattern of recurrence. Similar patterns of reflux after EVLA have been reported previously[253,341,423,427].

Whilst the notional level of at least 60 Jcm$^{-1}$ [406] is typically enough to give a durable closure of the main GSV trunk (92.1% at 2 years in Study 1), the data on clinical recurrence from Study 1, with support from the SFJ flush occlusion rates from Studies 3 to 5, suggest that additional energy should be focused at the SFJ; in principle by slowing the fibre withdrawal over the first 2cm. This may be more easily, and safely, achievable with the newer jacketed or radial-firing laser fibres compared to the original forward-firing bare fibre (see Fibre tip technology, p.218). The data on SFJ reflux up to 12 weeks from studies 3 to 5 show that technical success here is unrelated to either proximal GSV diameter or overall LEED.

Consideration of the ClosureFast RFA procedure gives further evidence for the importance of delivering higher energy at the SFJ and proximal GSV. This technique typically employs a "double treatment" of the first 7cm segment of ablation. This has been calculated to equate with a mean (SD) LEED of 116.2 (11.6) Jcm$^{-1}$ for the first treatment segment, with 68.2 (17.5) Jcm$^{-1}$ for each subsequent segment[344]. As a consequence of this higher energy dose, a 100% ablation of proximal GSV reflux was achieved immediately after the procedure[344]. This policy of increased proximal GSV energy delivery is supported by earlier data[428] that showed the majority of GSV recanalisations occurred in the first 12 months and developed in the GSV proximal to

the posterior thigh circumflex vein at the SFJ. There was no significant evidence of truncal recanalization either in the long-term from Study 1, or in the relatively short follow-up of studies 3 to 5 in this thesis. A previous meta-analysis included six studies that reported recanalization rates ranging from zero to 4.8%[429] at mean follow-up of 6 to 19 months.

The majority of surgeons who practice EVTA deliberately commence ablation approximately 2-3cm distal to the SFJ, leaving a patent proximal "stump" of GSV, which typically receives drainage from the other SFJ tributaries. This practice of ''ignoring the SFJ'' in EVTA procedures introduced a paradigm shift in the concept of treating patients with SVI. In the technique's infancy, the opinion of many was that performing endovenous ablation of the GSV without dissection of the SFJ violated a cardinal rule in superficial venous surgery, which is that the SFJ should be dissected, with each of the tributaries ligated and divided beyond their primary or even secondary divisions[430]. Hence, early reports of EVTA combined truncal ablation with a groin dissection[361,367]. However, it has become unquestionably apparent that the development of recurrent varicose veins after conventional surgery is significantly associated with the previous groin dissection as also seen in the Surgery group of Study 1 (above). The addition of groin dissection and SFJ ligation to EVTA procedures has consequently become redundant.

However, those patients in Study 1 who had successful flush SFJ occlusion with EVLA have neither demonstrated neovascularization nor clinical recurrence secondary to incompetent proximal tributaries. Hence, it would appear that the concept of "ignoring the SFJ" in EVTA appears flawed. This concern has also been raised in a consensus document on the reporting of EVTA[146], and a recent Cochrane review of endovenous ablative treatments for SVI[278].

Neovascularisation was not encountered in any of the EVLA group patients during two-year follow-up. Other studies have also shown this phenomenon to be very small or non-existent after EVTA[339,342,379,426]. This finding would lead to a hypothesis that in patients who do develop neovascularization following EVLA, it is attributable to vein wall perforation, with thermal injury to the surrounding tissues; angiogenesis is a feature of all healing wounds[431]. It may be argued that a policy of deliberate higher energy deposition at the SFJ in order to achieve a flush occlusion would risk a higher possibility of perforation and surrounding tissue damage that could consequently

provoke neovascularization. However, diligent tumescent infiltration, coupled with newer EVLA technologies such as higher wavelengths and advanced fibre technologies (see Fibre tip technology, p.218) should negate this concern and render neovascularization an even rarer entity in EVLA.

Concern has been raised that ablating the GSV flush at the SFJ may lead to higher rates of post-EVTA DVT or "endovenous heat-induced thrombosis" (EHIT). This hypothesis was not observed in any patient followed up for this thesis; no DVT was found in any patient at any time-point in any of the studies. Other good-quality contemporary studies have equally failed to show a single VTE episode following EVTA[417], although they were not aiming for a flush SFJ occlusion. The protocol in this thesis was to perform DUS at one week follow-up, whereas the majority of studies that report high rates of EHIT perform postprocedural DUS at 24-72hours; this raises questions about the relevance and natural history of EHIT, as others have also discussed[432].

EHIT is defined as the propagation of thrombus from a superficial vein to a deep vein, following EVTA[433], and is graded in severity from EHIT I to IV. EHIT type I involves thrombosis to the level of the superficial-deep junction and is deemed clinically insignificant; type II involves thrombus extension into the deep venous system with cross-sectional area less than 50%; type III involves thrombus extension into the deep venous system with cross-sectional area greater than 50%; type IV is total occlusion of the deep vein.

A recent paper[434] sought to elucidate the risk factors associated with post-EVLA DVT. The authors reviewed 360 consecutive EVLA procedures, including GSV and SSV. Patients received 810nm, 14W continuous EVLA via a 600μm bare-tipped fibre under tumescent anaesthesia. The policy was to aim for a 2cm proximal stump at the SFJ/SPJ. The overall rate of DVT (defined by the authors as type II-IV EHIT) was 5.27%, all discovered within one week of the index procedure. No patients had specific symptoms of DVT, nor did they develop any further adverse outcomes. Risk factors found to significantly increase the rate of "DVT" were age over 66 years, female gender and a history of superficial venous thrombosis (ORs of 4.1, 2.6 and 3.6, respectively); laser catheter tip position had no bearing on the risk of EHIT/DVT. No patient in this study received prophylaxis against VTE; in certain individuals in the NHS, those risk factors would likely result in the patient receiving prophylactic

LMWH, and hence DVT may have been avoided in some cases. Similar findings were reported from an earlier study[435] of EHIT after RFA of the GSV. Again, a policy of leaving a 2-3cm GSV stump was practiced. The authors reported a 2.7% incidence of type II EHIT. There was no correlation between catheter tip distance from the SFJ and the risk of EHIT. A further study found the only risk factor for developing EHIT after SSV EVTA was previous DVT[436].

Logically, the practice of deliberately leaving a patent proximal stump of GSV at the SFJ may in fact *predispose* to thrombotic events, in keeping with the principles of Virchow's triad (hypercoagulability, haemodynamic change (stasis or turbulence) and endothelial injury). Achieving a flush occlusion would leave no reservoir in which thrombosis could develop. This hypothesis is as yet unreported in the literature.

### Treatment of Below-knee GSV reflux

4 of 16 clinical recurrences at 2 years in the Study 1 EVLA group were attributable to below-knee GSV reflux, with a further 6 patients having GSV reflux and clinically-apparent varicosities below an incompetent mid-calf perforator communicating with the below-knee GSV. Residual below-knee GSV reflux at 2 years was a significant predictor of recurrence on logistic regression in both the Surgery (OR 3.659, p=0.005) and EVLA (OR 4.755, p=0.007) groups. This is despite all patients undergoing concomitant ambulatory phlebectomy of clinically apparent varicosities during the primary procedure. This untreated below-knee GSV thus seems to act as an occult reservoir of incompetence from which future clinical recurrence may develop.

It was practice at the start of the HELP-1 RCT for the EVLA technique to essentially mirror that of surgery; most GSV access sites were perigenicular (akin to the stripper exit site), regardless of distal reflux. Over time, the policy shifted to eradicate all demonstrable axial reflux, a tactic that has been borne-out by RCT data; ablation of the entire length of incompetent GSV from the lowest point of demonstrable reflux resulted in a 4-fold reduction (61% to 17%) in the requirement for delayed foam sclerotherapy of varicosities[437]. This 4-fold difference is broadly similar to the ORs reported above.

In their RCT of conventional surgery versus EVLA, Rasmussen *et al*[253] reported a clinical recurrence rate of 26% at two years after EVLA, which was not statistically

different to the surgery group (37%). In that study, no EVLA procedures treated the below-knee GSV and the authors acknowledged that some cases labeled as "recurrence" may actually have been "residual" varicosities. In the HELP-1 RCT, there was a progressive move toward below-knee GSV ablation at the latter end of the study, and all clinical recurrences were carefully delineated from residual varicosities. This may account for the differences in recurrence rates between the studies.

The DUS-confirmed ablation of treated GSV and vein shrinkage rates observed in Studies 3 to 5, where the policy was to ablate all demonstrable reflux, support the assertion that primary treatment of below-knee GSV reflux should prevent future recurrence from this source. Furthermore, there is a considerable association between below-knee GSV reflux and CVI[22], which is known to have a more deleterious impact on QoL than uncomplicated SVI[148,149]. Below-knee GSV EVLA can be safely performed with out any increase in complications, patient pain or morbidity[410,437].

It would therefore appear that simple technique modification to the EVLA procedure is likely to further reduce potential for clinical recurrence, which is already significantly lower than after conventional surgery. Consideration of a "composite" outcome for overall treatment failure based on primary failure, clinical recurrence and DUS-detected neovascularization or residual GSV reflux would further tip the balance more heavily in favour of EVLA over Surgery.

## Other EVLA Technique Modifications

The technique modifications described above are aimed at reducing long-term clinical recurrence rates, and consequently improving QoL, clinical severity and patient satisfaction. This thesis examined a number of other factors that may provide additional patient benefit in both the short- and long-term.

## Tumescent Anaesthesia

As described earlier, tumescent anaesthesia is key to the success of EVTA; attempts at EVTA prior to its adoption resulted in unacceptably high complication rates[333]. The technique of tumescent anaesthesia has its origins in the development of liposuction, which was first introduced in Rome in 1976[438], with further development in France[439].

These early liposuction techniques, which required GA for adequate pain control, were performed "dry" and were beset by high complication rates due to excessive blood loss and fluid shifts, and a protracted recovery time. Jeffrey Klein, an American dermatologist, introduced the "super wet" or "tumescent" technique for liposuction in 1987[385,440]. This technique involved the infiltration of large volumes of dilute lidocaine and epinephrine and removed the need for GA, virtually eliminated the requirement for blood transfusions[441], and decreased patient recovery time[442].

The benefits of tumescent anaesthesia are related to both the physical properties in terms of high tissue pressures and the chemical properties of the constituents: LA and epinephrine.

### Mechanism of action of LA

LAs are membrane-stabilising drugs that reversibly inhibit action potentials and hence nerve signal conduction via blockage of sodium influx through neuronal cell membrane voltage-gated sodium channels. Nerve diameter and the degree of myelination result in differing susceptibilities to the strength LA activity; unmyelinated small-diameter fibres, such as type C pain fibres, are the most sensitive to LA, whereas heavily myelinated, thicker fibres, such as type A motor fibres, are less sensitive to the effects of LA. Hence patients who have received LA do not experience pain or discomfort, but generally have maintained awareness of movement and retain functional ability.

### Safe dosage

The traditional teaching concerning the maximum safe dosing of lidocaine with epinephrine for dermal or local infusion is 7 mg kg$^{-1}$ [443]. However, using the tumescent technique, lidocaine doses of 35 mg kg$^{-1}$ were shown to be safe and effective by Klein[444], with a further study showing that dosages up to 55 mg kg$^{-1}$ can be used with minimal risk of lidocaine toxicity[445].

The toxicity of LA relates to plasma concentration; the more free LA in the body plasma, the greater the toxicity. The very dilute nature (typically 0.1%) of lidocaine in the tumescent solution, the relatively avascular compartment into which it is infiltrated (particularly given that the axial vein will be ablated), the vasoconstrictive effect of epinephrine, the high lipid solubility of lidocaine and its strong binding affinity to

adipose tissue surrounding the superficial axial veins, and the vascular compression due to tissue tumescence all combine to delay systemic uptake of lidocaine[446,447]. The target volume of tumescent infiltration in this thesis was 10ml per cm of GSV to be ablated, paying particular attention to the SFJ and proximal GSV, with an additional volume of typically 200ml for ambulatory phlebectomy. Infiltration of this volume of fluid gives good "tumescence" of the tissues, with a characteristic *peu d'orange* appearance of the skin. High tissue-pressure combined with epinephrine is shown to significantly reduce the systemic absorption rate of lidocaine[448].

The peak plasma concentration of lidocaine has been shown to be at around 8-12 hours after infusion. While some authors have seen a linear relationship between the dose of lidocaine infused and the peak plasma concentration[445,449], this has not been seen by others[450]. In a study where the mean (SD) dose of lidocaine was 33.2 (1.8) mg kg$^{-1}$ [450], the maximum peak plasma concentration was 3.3 µg ml$^{-1}$; objective clinical symptoms of lidocaine toxicity become apparent at plasma concentrations above 5 µg ml$^{-1}$ [451].

The dosage of lidocaine delivered to patients in Studies 3-5 in this thesis ranged from 3.51 to 15.63mg kg$^{-1}$, well below the values reported above. Furthermore, infiltration is typically performed in two stages; one for the perivenous tumescence for GSV EVLA, followed approximately 5-10 minutes later by infiltration for ambulatory phlebectomy. This will further reduce the overall peak plasma concentration as the full LA dose is not administered in a single bolus. Lidocaine is an amide anesthetic that is rapidly and efficiently eliminated by hepatic metabolism via the cytochrome P450 enzyme CYP3A4[452], hence a degree of caution should be taken when considering very high volumes of this tumescent anesthetic solution in patients who are taking known inhibitors of CYP3A4, or who have known significant liver disease.

### Pain of LA infiltration

One of the common problems of LA is the pain of infiltration, which is typically described as a burning or stinging sensation, and can be extreme enough for patients to be dissatisfied with the procedure and decline further LA procedures[391,453]. The pain associated with LA infiltration is predominantly due to the hydrogen ion concentration ([H$^+$]) within the solution, which results in an acidic pH[454]; this acidic pH is required for maintenance of a long shelf-life. The list of excipients in Xylocaine includes numerous acidic compounds, including hydrochloric acid and sodium metabisulphite.

The data from Study 2 show that off-the-shelf 1% Lidocaine with epinephrine has a pH of 4.38, and that even when diluted to 0.1%, the solution remains significantly below physiological pH at 6.32; 0.9% NaCl is itself slightly acidic at pH 6.55.

### Buffering of LA

The concept of using sodium bicarbonate ($NaHCO_3$) to buffer lidocaine to a physiological pH in order to reduce the pain of infiltration was first reported by McKay *et al*[455]. Whilst this remains an "off-license" use of $NaHCO_3$, the practice has become commonplace in a wide variety of anaesthetic techniques and interventional procedures from epidural anaesthesia, the emergency department, LA for intravenous cannulation and other minor procedures to various operative surgical applications[393,456-461]. There have been no reports of complications or adverse events associated with the buffering technique, nor has the technique been associated with drug precipitation[394,462].

A previous study showed that the addition of $NaHCO_3$ to lidocaine altered the pH of the solution more than could be explained by simple dilutional effects[463]. This finding was also reported in a Cochrane review of buffered versus unbuffered LA[394] (see below).

The pH results from Study 2 and the clinical pain scores from Study 3 may not be generalisable to other LA formulations, given that lipid-solubility may also have a role in the pain of infiltration. In addition to ameliorating the painful effects of an acidic pH, it has been shown that $NaHCO_3$ also potentiates LA activity by increasing the proportion of the non-ionised, lipid-soluble, component. This more readily crosses neuron cell membranes thus resulting in a speedier onset of LA action[392,464,465], without affecting its depth or duration of action[466]. A previous study[466] found a pH of 4.46 for 1% lidocaine with 1:200,000 epinephrine, while buffering with 10:1 LA:8.4% $NaHCO_3$ yielded a pH of 7.49. The manufacturers of the solutions used in that study were different to those used in this thesis, but very similar pH results were observed for both the unbuffered and buffered solutions. In the Cochrane review[394] the mean (SD) pH of 1% lidocaine buffered with 10:1 LA: 8.4% $NaHCO_3$ was 7.3 (0.2); also very similar to the results from Study 2.

The pH testing in Study 2 was performed with maintenance of a stable temperature that corresponded to the ambient temperature (21˚C) of the operating room where

EVLA is performed; this is important given that temperature can have a significant bearing on pH. Acidic solutions tend to increase in pH with increasing temperature, while the opposite is true for alkali solutions and neutral pH solutions tend to remain stable[467].

Hence, slightly less buffer might be required for solutions at a higher ambient temperature. The findings of several RCTs and a meta-analysis that infiltration of warmed LA appears to be better tolerated than cold or room temperature LA[468-470] would seem to corroborate this clinically. Therefore, as an alternative to buffering, or to reduce the amount of buffer required, the tumescent solution could be heated to 37°C. However, this would require use of a warmer cabinet and advance preparation of the tumescent solution, which may not be practical or an efficient use of time. Furthermore, the cooler solution potentially has more protective effects against EVTA heat-induced tissue damage than warmer solutions (see below).

It may be that more accurate titration of $NaHCO_3$ at a specific temperature reveals an even more optimal pH. In practical terms, however, the addition of 10ml $NaHCO_3$ for every 1000ml 0.1% Xylocaine with 1:2000,000 epinephrine is appropriate given that this equates to one full vial per preparation. The cost of $NaHCO_3$ is almost negligible[443] in comparison to the overall expense of an EVTA procedure.

A Cochrane review[394] found that the addition of $NaHCO_3$ to lidocaine with epinephrine, used for intradermal local anaesthesia, resulted in a mean reduction of pain scores by 24.6mm (95% CI: 1.72-3.2) on a 100mm VAS, when compared with the unbuffered equivalent; both versions were given at room temperature. This difference was larger than for LA solutions without epinephrine, based on the lower pH of solution that results from the addition of epinephrine, as demonstrated in Study 2.

The addition of epinephrine is highly advantageous in tumescent anaesthesia, particularly in the context of ambulatory phlebectomy, which, as demonstrated in Study 4, ought to be considered the optimal concomitant treatment for varicosities after truncal EVLA (see below, p.212). Infiltration of tumescent anaesthesia facilitates predissection of the vein to be removed from surrounding tissues, and lifts it closer to the skin, it compresses capillaries for improved haemostasis and less postoperative bruising. A retrospective review of 94 consecutive patients undergoing ambulatory

phlebectomy with epinephrine-containing tumescent anaesthesia[471] reported significantly reduced rates of haematoma (0% versus 3.5%) and hyperpigmentation (0% versus 3.6%) in comparison with an earlier cohort of patients from the same group[472] receiving the same procedure without epinephrine. The constituents additionally provide cleansing and antimicrobial cover to the phlebectomy sites; interestingly, $NaHCO_3$ is reported to augment this antimicrobial activity of LA[473].

The difference in the primary outcome measure of periprocedural pain scores between buffered and unbuffered tumescent anaesthesia in Study 3 appears to be even greater than that reported in the Cochrane review, given that patients are receiving larger-volume perivenous tumescent anaesthesia rather than just a single intradermal injection. The review also demonstrated that patients expressed a preference for buffered solutions, indicating that this difference in pain scores is clinically significant. A previous study[474] suggested that the minimum clinically relevant difference in acute pain scores is 13mm on a 100mm VAS.

With respect to sample size calculation for a RCT, given an α of 0.05 and power of 90%, 43 patients would be required in each arm to see this size of effect; 50 patients in each arm would allow for a 15% attrition rate. Based on this power calculation and data from Studies 2 and 3, a RCT of buffered versus unbuffered tumescent anaesthesia is now underway at the Academic Vascular Surgery Unit, Hull, after securing REC, MHRA and R&D approval.

The precise details of tumescent anaesthesia in EVTA have generally been poorly reported in the literature. The pH of the tumescent anaesthetic solution has not previously been studied in the context of EVTA; several studies have recently reported the use of $NaHCO_3$ to buffer the solution, but the specific pH was not reported[475,476]. The data on tumescent anaesthesia from Studies 2 and 3, coupled with specific knowledge of the pharmacokinetics lends strong support to a policy of more accurate and open reporting of the technique used in future studies, such as the constituents of tumescent anaesthesia, use of buffering and corresponding pH, volumes infiltrated and temperature of the solution in order that studies can be more directly compared. The CLASS trial specifically collected some of this information, and hence further analysis of the optimal tumescent anaesthesia parameters might be possible in that study.

*Alternative Tumescent Techniques*

Chong *et al*[477] reported the use of infiltration of saline at 4°C ("cold saline infiltration") as an alternative to tumescent with LA. This was a case series of 12 patients, with no objective assessment of pain, patient satisfaction or QoL. There have been no comparative studies of this technique. Furthermore, the authors report using this technique for EVLA alone, rather than also providing anaesthesia for phlebectomy, as per standard practice. This technique would therefore require separate preparation of tumescent anaesthesia with LA for phlebectomy, which seems rather inefficient.

Pannier *et al* reported a RCT of cold (5°C) versus warmed (37°C) tumescent anaesthesia during 1470nm EVLA[478]. Post-procedural pain was measured on a VAS of 0-4 up to day 10, with mean pain scores on days 2-10 of 1.0 and 1.2 (n.s.) for the cold and warm groups respectively. Unfortunately, periprocedural pain was not assessed.

A recent *in vitro* study compared the vein perforation rates of 980nm and 1470nm wavelength lasers, using both room-temperature and cooled tumescent anesthesia[479]. There were fewer vein perforations with both wavelengths using cold (4°C) tumescent in comparison to room temperature (24°C) tumescent (p=0.006). There were further advantages of using the higher-wavelength laser (see below, p.215). It is not known whether these *in vitro* findings of reduced vein perforation translate into a significant difference in *in vivo* clinical outcomes such as less pain, or whether some other function of laser activity accounts for the clinical differences. Furthermore, reduced pain secondary to perforation may be offset by the increased infiltration pain of a cold versus warmed solution, as discussed earlier[468-470].

## Concomitant ambulatory phlebectomy

As discussed earlier, while many surgeons elect to delay treatment of varicosities after EVTA, the best available evidence lends support to a policy of concomitant treatment. At least 40% of patients require delayed treatment of varicosities if not treated concomitantly[488]. In the RCT of EVLA alone versus cryostripping[360], 62% of patients in the EVLA group had clinically apparent varicosities at 6 weeks; all underwent liquid sclerotherapy. In the RCT by Darwood et al[359], delayed injection sclerotherapy

to varicosities was performed at 6 weeks, if requested by the patient. 46% of patients requested sclerotherapy, with 10% undergoing more than one session. It is not clear how significant any residual varicosities were in the patients not undergoing sclerotherapy, whether they would have further benefitted from a concomitant procedure, and what the long-term sequelae of untreated varicosities are. What is known, however, is that secondary procedures are unpopular with patients, with 71% wanting full treatment of their varicose veins in a single visit[383]. This makes treatments with a common requirement for re-intervention a poor standard of care. A one-stop single treatment seems attractive to both patients and surgeons alike[373,400].

Until now, there have been no comparative studies of the two treatment options for varicosities (ambulatory phlebectomy and foam sclerotherapy) within this context, as highlighted by the recent NICE guidelines[228]. Study 4 demonstrates significantly better VCSS and AVVQ scores in the AP group at 12 weeks. These subtle differences are likely to equate with small but significant clinically-important modifications in multi-society guidelines on the use of EVTA, which acknowledge that clinical success is dependent on the thoroughness of the adjunctive procedures in addition to the success of the EVTA[332].

The RCTs performed by Kalteis *et al*[361] and Rasmussen *et al*[358], discussed earlier, both included concomitant AP. The rates of reintervention were not quoted. In both studies, it is suggested that the AP may have contributed significantly to the postprocedural pain. However, the post-procedural pain scores in Study 4, which were no different between the AP and foam groups, would seem to contradict that assertion. The short-term difference in QoL between surgery and EVLT is likely due to groin dissection & stripping rather than phlebectomies[399].

Complications following either concomitant treatment in Study 4 were relatively infrequent, with a trend toward less phlebitis after AP. In the Dutch study of AP versus foam sclerotherapy of the anterior thigh circumflex vein[401], the occurrence of telangiectatic matting at 2 years was significantly higher following phlebectomy, while the sclerotherapy group had a higher incidence of phlebitis (27% versus 12%), but this did not reach statistical significance (p=0.07). There were no differences in the rate of haematoma. This study reported blistering in 31% of the AP arm, which is significantly higher than reported in other large series of AP and in the studies within this thesis. A review of 1000 consecutive cases of AP[402] identified a very low

complication rate; the most frequently encountered complications were minor: blister formation (1.3%), phlebitis (1.1%), telangiectasias (0.5%), hyperpigmentation (0.4%) and temporary sensory nerve damage (0.2%). Hence, AP in experienced hands is an extremely low-risk procedure.

Alternative techniques to multiple stab phlebectomy in the context of conventional surgery have been reported, such as trans-illuminated powered phlebectomy (TIPP). However, RCT evidence suggests the latter technique results in greater postoperative bruising and pain[489]. It would be seem likely that the TIPP technique would fare even more poorly in comparison with AP within the context of adjuvant treatment of varicosities in EVTA under tumescent anaesthesia.

Further follow up of the patients in Study 4 will hopefully identify whether the subtle short-term advantages of AP over foam translate into a meaningful difference in longer-term outcomes.


## EVLA Energy Delivery

Over a decade after the introduction of EVLA, there is still a relative lack of understanding concerning the underlying physics and the tissue interactions it creates. This has hindered progress on fine optimization of the technique, reflected by the fact that no single protocol for its use exists, unlike that for ClosureFast.

The optimal treatment window of SVI by EVLA is a balance between depositing energy in the tissues of high enough magnitude to produce a durable ablation, yet low enough to minimize unwanted effects; both recurrence and downtime secondary to complications are unpopular with patients. The data from this thesis and discussion below suggest that power is not the sole determinant of success, but that different wavelengths have different tissue interactions and require different power settings, while advances in laser fibre tip design may further influence energy delivery and the tissue response.

Progress toward reaching consensus on one or a few optimal EVLA procedures thus requires continuing research such as *in vitro*, ex vivo and *in vivo* experiments and modeling of EVLA-related mechanisms.

The aim of Study 5 was to assess whether a higher-wavelength laser is associated with less post-procedural pain than the existing lower-wavelength device. The postprocedural pain data do show a significant advantage of 1470nm over 810nm wavelength laser, in keeping with other studies[490,491]. This is further supported by the significantly lower analgesia requirements in the 1470nm group. In addition to the better pain scores, there was suggestion of a modest lowering in the overall complication rate with 1470nm laser, although the total numbers were small.

In an ideal model, all other treatment parameters would be kept identical in order to be sure that any difference could be attributed solely to the change in wavelength. 810nm EVLA has been shown in other studies to give an optimal ablation when using a power of 14W[403]. Increasing laser wavelength significantly increases the depth of tissue penetration and the energy deposition per unit volume; 1470nm laser has a five-fold greater tissue absorption and penetration than 810nm wavelengths[355,492]. There was therefore great concern that equivalent power at 1470nm would result in too high a LEED, consequently increasing complication rates due to greater tissue destruction. This concern was shown in earlier work[411] and confirmed by the manufacturer (Angiodynamics, Cambridge, UK)[493], who recommended 8W continuous power, aiming for a LEED of around 50Jcm$^{-1}$ for the 1470nm device.

In practical terms, these power settings allowed for the same catheter pullback speed as with the 810nm device (given that 1 Watt power equates to 1 Joule per second). Study 5 was therefore a pragmatic study, using the EVLA devices as per the best available data. All other potential variables in the study were kept constant; baseline clinical, QoL and DUS parameters, length of vein treated, the aim for flush SFJ occlusion, volume of tumescent anaesthesia used, laser fibre (NeverTouch jacketed fibre) and use of concomitant phlebectomy were the same for both groups.

Early studies of higher-wavelength EVLA sought to assess whether the hypothesized lower rate of vein perforation allowed the procedure to be performed without tumescent anaesthesia[494]; this was shown to be unachievable with the currently available technology. Experimentation using an *in vivo* goat model[495] revealed the importance of tumescent anaesthesia and eradication of intraluminal blood prior to higher wavelength EVLA. 1500nm EVLA was performed in either reverse Trendelenburg position, Trendelenburg position, or Trendelenburg position plus the

infiltration of perivenous tumescent solution. The latter technique resulted in a significant decrease in the volume of intraluminal blood. Histological examination 1 week post-ablation identified that reduced intraluminal blood significantly correlated with greater vein wall destruction. Tumescent anaesthesia therefore remains key to the success of the EVLA procedure, perhaps even more so with higher-wavelength lasers, thus reinforcing the earlier discussions on the importance of minimising the pain of tumescent infiltration.

Using 810nm 14W continuous laser, successful, long-term GSV occlusion is achieved with a LEED of around 80-100J cm$^{-1}$. Little work has been performed to assess the optimal LEED for higher wavelength lasers. Comparing the vein shrinkage rates between 810nm and 1470nm EVLA in Study 5 seems to suggest that the significantly lower power settings with the higher wavelength laser are sufficient to provide a durable ablation.

A recent *in vitro* study identified fewer vein perforations with a 1470nm model in comparison to a 980nm equivalent, using both cold and room-temperature tumescent solutions (p=0.0194)[479], which may explain the reduced postoperative pain seen in Study 5. However, that study failed to report power settings or LEED for either wavelength, hence it is difficult to be certain whether the energy deposition was sufficient, or possibly excessive, for successful ablation.

Duman *et al* recently reported a cohort study of the effect of EVLA wavelength on postprocedural pain[476]. 980nm (14W continuous) and 1470nm (10W continuous) lasers were assessed. The authors found no statistically significant difference in post-procedural pain between the two wavelengths. However, the power used for the 1470nm device (10W) was higher than used in Study 5 (8W); this may have led to greater vein perforation rates, and hence increased postprocedural pain. The first successful results with 1470nm EVLA were published in 2009 by Pannier et al[496], using 15W continuous power with a LEED of around 100Jcm$^{-1.}$ It seems likely that those power settings were excessive, substantiated by the fact that the reported paresthesia rate was 9.5% persisting beyond 6 months and 7.6% after 1 year, much higher than the short-term rates observed with either 1470nm or 810nm EVLA in this thesis.

In the RCT of RFA, EVLA, UGFS and conventional surgery by Rasmussen et al[417], 980nm laser was used for the first 17 patients, with 1470nm used for the subsequent 108 patients. In a subgroup analysis, there were no significant differences in postprocedural pain scores between the two wavelengths. However, there was significant methodological heterogeneity across the EVLA group, with both continuous and pulsed modes used. Bilateral treatment was undertaken where indicated, but it is not reported which patients received this. Furthermore, the power settings for each device are not reported; a mean LEED of 76.5Jcm$^{-1}$ is reported, but given that the majority of patients received 1470nm EVLA, that seems higher than required. Additionally, the investigators used a bare fibre for all patients, rather than a more advanced fibre, which may also have had a negative impact on pain.

An opposing view to the assertion that the higher wavelength is the key difference would be that it is actually the power setting (Wattage) that is important. In order to assess this, the 810nm device could be used with significantly lower power. However, given the above discussion that 80Jcm$^{-1}$ is generally considered the required LEED for 810nm EVLA, this would require a significantly protracted treatment time and would not be practical.

### LEED or Fluence?

Much of the above discussion regarding energy delivery concerns linear endovenous energy density (LEED, Jcm$^{-1}$). Proebstle et al[347,404] argued that this is an oversimplification of energy deposition, and that the vein diameter should be considered. This concept gave rise to the term "endovenous fluence equivalent", EFE (Jcm$^{-2}$).

However the idea of EFE is possibly flawed, given that vein diameter at the time of EVTA is significantly reduced due to catheter-induced spasm and the effects of tumescent anaesthesia as discussed earlier. Furthermore, neither healthy nor diseased vein is of a uniform diameter throughout its length, making the calculation more difficult. The DUS data concerning flush SFJ occlusion from Study 1 and Studies 3 to 5 clearly show that greater energy deposition is required at the proximal GSV; this may be a reflection of greater hydrostatic forces at the SFJ, or a subconscious hastening of the initial catheter withdrawal for fear of damaging the deep vein. Hence, adopting the principle of EFE would achieve this greater energy density.

There are currently no robust data to suggest a relationship between vein diameter and technical success in EVTA. The CLASS trial has a maximum allowed GSV diameter of 15mm; although few patients exceed this size, they have been successfully treated in this thesis. The DUS data show that success is not predicted by the baseline proximal GSV diameter.

Adopting the EFE principle would also lead to reduced energy deposition in the below-knee GSV, which is typically of smaller calibre than the proximal segment. There is no robust evidence to suggest that smaller-calibre veins require less energy for successful ablation, while there is some evidence to suggest that increased LEED *per se* does not directly influence post-procedural pain or complications[347,410].

Over the course of this thesis, there was a gradual increase in the length of GSV treated and LEED administered, in light of the findings from Study 1, as also demonstrated in a recently published report from the Academic Vascular Surgical Unit in Hull[497], without any apparent increase in post-procedural pain, complication or adverse event.

Within the context of energy delivery, perhaps one of the attractive aspects of EVLA over other techniques such as ClosureFast is the ability to tailor a treatment for the individual patient; as alluded to earlier, ClosureFast does not offer that flexibility.

### *Fibre tip technology*

Early laser fibre tip design was simply a "bare" optical fibre, as used in Study 1. This design has been implicated in focal charring and vein perforation due to direct contact between the forward-firing tip and the vein wall. Further developments in technology have included the jacketed, tulip-tipped and radial-firing fibres. The jacket-tipped and tulip fibres are designed to prevent direct contact with the vein wall, while radial fibre evenly distributes the laser beam over 360°.

Studies 3 to 5 used the NeverTouch® fibre (Angiodynamics, Cambridge, UK). This comprises a glass weld at the distal tip of a 600μm fibre, resulting in an effective fibre diameter of 905μm, hence lowering the power density at the tip by 56% compared to a standard bare-tipped 600μm fiber[498]. In combination with the gold jacket, which projects over the tip of the fibre, the net aim is to effect a homogeneous ablation with less focal charring of the vein wall that is typically seen with bare-tip fibres.

The radial fibre (Biolitec®, Jena, Germany) aims to deliver the energy out of the side of the fibre tip directly at the vein wall. Other designs exist and more are in development.

The aims of Studies 3 to 5 in this thesis were to each assess a single parameter change, whilst keeping other potentially confounding factors, such as the fibre tip (NeverTouch), constant. It may be that the response profiles across the studies would have been different using alternative fibre tip technologies. There has been no comparative study of the newer fibre technologies to date.

Schwarz *et al*[475] reported a prospective cohort study of bare versus radial-firing fibre tips using 1470nm EVLA. The primary outcome measure was the incidence of ecchymosis and bruising, which they referred to as "skin bleeding". Overall, the radial-firing fibre resulted in significantly reduced rate of "skin bleeding" and a subtle reduction in analgesia requirements. However, postprocedural pain was not directly assessed, nor was there an assessment of QoL. Furthermore, the power settings were not uniform across the groups; the bare fibre group received 15W power, with a mean LEED of 79.4Jcm$^{-1}$, while the radial fibre group received 10W power, (mean LEED = 57.4Jcm$^{-1}$). In the context of the wavelength discussion above, these power settings seem far too high, particularly for the bare fibre, which is known to have a more focused beam. The study may therefore have overplayed the advantages of a radial fibre.

## Clinical Outcomes

### Periprocedural Pain

Pain has often been cited as a complication of EVTA in the literature[499], although this is perhaps a misrepresentation, as all invasive procedures will be associated with some degree of pain or discomfort. The aim is to reduce this to an acceptable level that does not impact upon normal functioning or QoL. The discussion of tumescent anaesthesia above highlights ways in which periprocedural pain can be significantly reduced, given that this appears to be the primary source of discomfort. Further treatment modifications such as energy delivery (wavelength and fibre tip technology) are discussed above.

Whilst there was a normal distribution of pain scores in the unbuffered group of Study 3, those in the Buffered group were negatively skewed, indicating that the majority of patients had very low periprocedural pain scores. The AUC data from the ROC analysis also corroborate this finding.

During data analysis of pain scores for Study 3, there was an apparent significant difference between the scores reported by male and female participants. This analysis was not in the original aims of the study, and given the small numbers involved could represent type I error. The finding from Study 3 that men reported less periprocedural pain than women is a recognized phenomenon[500,501]. It has also been reported once in the venous literature[502], based on the results of a Dutch thesis. Evidence suggests this finding is a psychosocial attribute, rather than men physically experiencing less pain than women on an autonomic level[500,501]. This is undoubtedly a complex area of study, and outwith the scope of this thesis, hence no further discussion or conclusions on the individual gender data are appropriate.

Putting the periprocedural pain scores from Study 3 into context, other recent studies of EVTA techniques have shown similar, if not higher pain. Kabnick reported a mean pain score of 2.2 to 2.6 on a scale of 0 to 5 after EVLA[490]. In a study of ClosureFast using tumescent anaesthesia (comprising 50ml saline with 20ml 1% lidocaine with epinephrine), mean periprocedural pain was 4/10, with 40% of all patients recording a VAS score greater than 4[389]. Pronk *et al*[364] reported a mean (SD) VAS of pain during tumescent infiltration of 4.69 (2.48) using an unbuffered solution of 0.1% lidocaine containing epinephrine. Mean (SD) periprocedural pain was 3.39(2.57) and 2.21(2.40), p=0.02, for surgery and EVLA respectively.

A further study reporting periprocedural pain with ClosureFAST quoted mean (range) VAS scores of 3.1 (0-10) during the procedure, and 2.0 (0-10) after 1 week[503]. The tumescent solution used comprised 1L of normal saline, 50 mL 1% Lidocaine, 1 mg of epinephrine and 10 mL 8.4% $NaHCO_3$; there was no comment on pH of the solution. These pain scores seem quite high compared to those seen in Study 3, even for the unbuffered group.

### *Postprocedural Pain*

Studies 3 to 5 demonstrated consistently low post-procedural pain scores over the first week. There was a statistically significant benefit of 1470nm EVLA in comparison to

810nm EVLA in Study 5 (see Wavelength and Power, p.215).  The observed postprocedural pain scores after 810nm in this thesis were broadly similar to other studies following 810nm EVLA[378,389].  The postoperative pain data from Study 3 suggest that lower periprocedural pain may have a beneficial impact upon early postprocedural pain experience, with the Day 0 pain scores being significantly lower in the Buffered group than the Unbuffered group (p=0.033); there were no differences at any other time point, however.

Many studies have used post-procedural pain as the primary outcome measure.  This should be regarded as a flawed aim, as it does not consider technical success or freedom from recurrence, which are the concern of most patients.  No studies reporting postprocedural pain after EVTA have identified whether the differences are clinically significant.  However, the data from numerous recent studies[364,373,504] would suggest they are not, given the lack of difference in QoL or timing of return to normal activities.

Anecdotal experience from patients who decline recruitment into the CLASS trial suggests that many would prefer to trade a small increase in short-term pain (from either surgery or EVLA rather than UGFS) for greater surety of long-term success.

### Return to Normal Activities

The HELP-1 RCT has shown that patients take significantly less time to return to full activity and employment following EVLA than with surgery[274], a finding that has also been reported after ClosureFast[338,389] although others have failed to show this difference[337,358,417].  Neither peri- nor post-procedural pain appears to accurately correlate with time to resumption of normal activity, with tired or heavy legs being a more commonly cited reason in a previous study[389].  Return to work is reportedly influenced by numerous factors including employment and social status in addition to the specific treatment received[505,506]; the data from Studies 3-5 would seem to corroborate these findings

It was decided not to assess "return to work" as an outcome in Studies 3 to 5, given that this does not appear to be representative of return to normal activity; many patients were back to performing full activity long before they returned to work, for some of the reasons alluded to above, while many others were victim to the recession and were unemployed.

*Complications*

The complications in this thesis were classified in accordance with the Society of Interventional Radiology Standards of Practice Committee Guidelines on reporting complications[414]. This classifies bruising/ecchymosis, pain, induration, skin burns, dysaesthsia, superficial thrombophlebitis and haematoma as minor complications. VTE and nerve injury are classified as major complications. The most common side effects seen with all laser types are bruising, localized pain, induration and discomfort along the treated vein and superficial thrombophlebitis[507]. Infection also appears lower in endovenous procedures; the lack of groin incision is probably fundamental to this. As previously discussed, despite being classified as clean surgery, groin infection rates are high. Perhaps this is related to haematoma; a RCT of standard SFJ ligation versus flush ligation with inversion of the junction endothelium showed a significant difference in groin infection rates, which the authors suggest may be attributed to more fastidious haemostasis in the latter group[300].

There were no major complications identified in any of the studies within this thesis, with reassuringly low rates of minor complications. As discussed, there were some subtle differences in minor complication rates between concomitant ambulatory phlebectomy and foam sclerotherapy, and between 810nm and 1470nm laser wavelength. These differences may have become more significant in a larger sample size.

Bruising was not formally assessed in this thesis. Its occurrence was relatively mild and does not seem to correlate with pain or return to normal activity. The measurement of bruising or ecchymosis is highly subjective and variable, with no standardization of measurements. Various methods of bruising assessment following EVTA have been reported, such as digital photography[340] or Likert scale[374]. Evidence of a true correlation between bruising and pain is mixed; perhaps more importantly, QoL does not appear to be directly affected. De Medeiros *et al* showed significantly less bruising and oedema following EVLA in comparison to surgery, but there were no corresponding differences in pain scores[367].

Conversely, a RCT by Nordon *et al*[504] showed above-knee bruising to be significantly greater with 810nm 12W continuous EVLA via a jacketed fibre versus ClosureFAST (median (range): 3.85% (0-27.4%) versus 0.6% (0-11.5), $p < 0.001$ and also pain to be

greater with EVLA than RFA on each of the 7 postoperative days. However, the quoted pain scores following EVLA appear to be high, in comparison to this thesis and there is a great disparity between the data quoted in the text and the graphical representation. Tumescent anaesthesia in their study was produced from 1litre 0.9% NaCl containing an undisclosed amount of 1% lidocaine with 1:200,000 epinephrine, without pH buffering.

Proebstle *et al* reported that a 6.4% incidence of postprocedural ecchymosis after ClosureFast was likely due to tumescent anesthesia[344]. This does not seem a correct assertion given the discussions above. Neither the constituents nor volume of tumescent solution were reported.

The reporting of many complications is highly subjective, leading to significant observer bias in the literature[508]. Notwithstanding this issue, the complication rates do appear to have progressively fallen[507]. This is likely explained by numerous factors, including improvements in imaging technology and experience with its use, appropriate case selection, refinement of operative technique and the technologies utilized[499]. A recent meta-analysis of EVLA, ClosureFast and Surgery identified that EVLA had very low incidences of VTE (0.4%), infection (0.7%), paraesthesia (3.3%), superficial venous thrombosis (5.5%), haematoma (2.1%) and skin burns (0.7%). In comparison with Surgery, EVLA had significantly lower incidences of infection, paraesthesia, and haematoma[508].

## QoL

QoL and clinical recurrence appear to be intimately linked. The data from Study 1 show that patients who have clinical recurrence suffer significantly worse QoL than their recurrence-free counterparts. The proposed technical modifcations to further improve freedom from clinical recurrence after EVLA may therefore lead to greater long-term benefits in QoL over conventional surgery. As a result, the cost-effectiveness of the EVLA technique may become more attractive with time. Given that patients with clinical recurrence had significantly worse QoL, in association with lower VCSS and patient satisfaction, future clinical practice could potentially dispense with routine clinical or DUS follow-up and instead used PROMs to inform the need for formal reassessment in self-selecting individuals with suboptimal outcomes, hence further improving cost-effectiveness.

This thesis did not set out to assess cost-effectiveness, although given that cost-effectiveness is calculated from QoL data, factors that can improve patient tolerability and decrease clinical recurrence should ultimately improve cost-effectiveness further. However, as this thesis has shown, the generic tools are perhaps not sensitive enough to detect small but clinically-meaningful differences between variations in technique.

## Critique

All of the clinical studies performed within this thesis were non-blinded; the research group could be accused of being "enthusiasts" of EVLA, hence potentially introducing bias. Attempts were made to Potential bias secondary to the lack of blinding was minimised by the patients independently completing QoL and satisfaction questionnaires prior to contact with a researcher. Clinical assessment was undertaken using validated, objective measures such as VCSS and CEAP, thus further reducing opportunity for observer bias. True blinding of observers is difficult. For example, with the experience of DUS in the follow-up of SVI intervention comes the knowledge of how different treatment modalities appear over time.

Studies 3 to 5 were designed as pragmatic pilot studies performed during routine clinical practice to gauge the potential impact of the changes to standard EVLA parameters. Each of these studies is therefore limited by lack of randomization; any number of unknown factors may have had hidden influence on the study groups, which appeared otherwise well matched at baseline. Furthermore, it is difficult to know exactly what was the agenda of the patients seeking treatment, and whether or not they would have done so were certain treatment modalities not available. Selection biases may be considered more likely than for RCT data, although an attempt to minimize this was made by including consecutive patients from an unselected NHS outpatient referral system.

The numbers of patients assessed in the three cohort studies were also relatively small, potentially allowing for either Type I or II errors to occur.

Patient experience during EVLA may be influenced by a variety of factors that were not expressly studied in this thesis. Pain is shown to have a significant impact on early post-operative QoL and patient satisfaction; it is recognized that many factors aside from those studied in this thesis may contribute to pain and patient experience, beginning long before the patient enters the procedure room or operating theatre, continuing through the procedure itself, and beyond the immediate recovery period. These factors have the potential to act as confounding aspects in patient experience and therefore patient-reported outcomes. Where possible, attempts were made to keep each procedure uniform, as per the methodology, whilst ensuring each patient was actively engaged in their care and treated as an individual. The rate of tumescent anaesthesia infiltration, as an example, could be varied according to perceived patient tolerance. It is accepted that further work could be undertaken to assess various aspects of patient experience that could be changed or improved upon.

The extent of ambulatory phlebectomy (Studies 1, 3, 4 and 5) could not be controlled, and was not therefore recorded; all visible, symptomatic varicosities were marked preoperatively with the patient standing and providing their input. Thus there is potential for this procedure to act as a confounder for any peri- or post-operative pain, patient satisfaction and QoL. Similarly, the number of varicosities treated by foam sclerotherapy (Study 4) was not recorded, as the aim was to treat all varicosities, within the limits of maximum foam dose. However, all included patients within the studies in this thesis were taken from routine NHS referrals without prejudice and so there is no significant concern that the treatment groups were not representative of typical practice.

Whilst current evidence suggests that as a collective, patients benefit from concomitant treatment of varicosities, evidence from other studies suggests a significant proportion will improve with truncal ablation only, although the long-term sequelae of untreated varicosities are not well documented. As highlighted in the recent NICE guidance[228], further work is required to identify which patients will benefit from concomitant treatment, and which can be safely left without fear of dissatisfaction, in order to tailor the procedure to the individual patient.

The duration of post-procedural compression in the studies presented was longer than reported in many other studies and that recommended by the most recent NICE guidance[228]. Wearing bandaging for the first week, to be removed by an investigator at

follow-up, followed by compression hosiery until 6-week follow-up allowed for very low drop-out rates, however. It is not known whether such a long duration of compression may have had an adverse influence on QoL, although patient satisfaction levels at 12 weeks were high in all studies.

This thesis focuses purely on primary unilateral SVI attributable to SFJ/GSV reflux; patients with SPJ/SSV reflux were not included. The findings reported in this thesis may not therefore be directly attributable to patients with different patterns of disease to that studied, although it is known that this distribution of SVI accounts for the vast majority of patients. There is evidence to suggest that patients with SPJ/SSV disease have a difference in QoL response both to the disease itself, and to treatment, in comparison to patients with SFJ/GSV disease[149]. Hence the decision to keep a "pure" cohort of patients is defensible, so as not to add in potential confounding factors that might have blurred the outcomes in what is an already complex area of clinical research.

The procedures carried out in this thesis were performed by surgeons who have a special interest in SVI, and extensive experience in performing endovenous ablative procedures, hence there was no learning curve effect. All investigators had formal postgraduate university-accredited qualification in vascular ultrasound. Patients were seen by an experienced investigator in a "one-stop" venous clinic; full clinical and DUS assessment was undertaken in this appointment, along with informed counseling regarding potential treatment options, currently recruiting clinical trials. Innovations such as this clinic, with tailored treatment in every case, alongside the increased contact and support offered by the research team may have contributed to improvements in patient care and outcomes and very high levels of patient satisfaction as shown in the patient satisfaction VAS data. Close follow-up within a postprocedural package of care that included clinical and DUS expertise and a dedicated, experienced venous research nurse meant that high-levels of attendance were achieved. The responses from telephone calls made to non-attenders at two years in Study 1 suggested that these patients did not attend as they were happy with their outcome, rather than feeling disenfranchised.

Many previous studies of treatment for SVI have suffered from significant heterogeneity in the reporting of outcomes[330,515]. All the studies within this thesis used

well-validated, objective outcome measures, encompassing clinical, QoL and DUS parameters, based on international guidelines or consensus where available.

## Further avenues of research

The "endovenous revolution" has truly occurred; EVTA is accepted as a preferable alternative to conventional surgery for the treatment of SVI, with supporting data from a growing number of high-quality studies, as well as non-randomised experiences with new techniques. Recent NICE guidance[228] has recommended that EVTA should be the first line treatment for symptomatic SVI, followed by UGFS and finally surgery. There are, however, several aspects of endovenous treatment that do not have a significant evidence base.

In addition to continuing the longer-term follow-up of subjects studied in this thesis, data from multicentre randomized studies such as the CLASS trial are eagerly awaited; recruitment was slower than anticipated, due in part to many patients' preference for a less invasive procedure, with others opting for a more "conventional", "well known" operation. This was also a point commented upon in the study by Darwood *et al*[359]; 60% of patients declining randomization expressed a preference for EVLA, while 36% wished to receive surgery. During this time, a number of technical modifications to EVLA have taken place, such as greater attention to tumescent anaesthesia, transition from lower to higher wavelength lasers and bare to jacketed or radial-firing fibres. It will be interesting to see the subgroup analyses for these factors within a larger cohort of patients across multiple centres.

### Recurrent SVI

A large area that is yet to be studied in detail is EVTA for recurrent varicose veins, which account for about 20% of venous procedures, but are associated with higher levels of complication, morbidity and patient dissatisfaction. The use of hybrid endovenous procedures, such as catheter-directed UGFS of groin neovascularization plus EVLA of residual or recurrent truncal reflux seems attractive in comparison to redo open surgery.

### Venous Ulcer Disease

The ESCHAR study[241] has previously provided evidence that intervention for SVI in the context of venous ulceration can reduce recurrence rates. The population concerned is typically frail or elderly with significant comorbidity and many are not

suitable for, or do not wish to undergo conventional surgical intervention. A study of EVLA under local tumescent anaesthesia therefore seems attractive in this context. The number of patients with C5-6 disease treated in this thesis seems lower than the predicted prevalence rates from epidemiological data, yet there were no exclusions to their treatment. This suggests a problem with referral of such patients from primary care, which would need to be addressed in order to achieve sufficient recruitment for such a study. A recent Cochrane review of EVTA for venous ulcer disease[516] was unable to identify any RCT evidence in this area.

The Early Venous Reflux Ablation (EVRA) multicentre RCT[517], recently commenced recruitment of patients with venous ulceration to receive either standard compression therapy or endovenous ablation (any method) within two weeks of randomization, plus standard compression. The primary outcome measure is time from randomization to ulcer healing. It will be interesting to see whether there are any differences in treatment outcomes between the endovenous therapies.

### *Postprocedural duration of compression therapy*

The recent NICE guidelines[228] recommend not continuing compression therapy for longer than one week following venous intervention. This would represent a significant change in practice for many vascular centres. There is no robust evidence to suggest what is the optimum duration for postprocedural compression.

# Conclusions

Study 1 provides further evidence of the superior clinical efficacy of EVLA when compared to conventional surgery for the treatment of primary, symptomatic GSV reflux, giving rise to fewer clinical recurrences at two years. A number of the analyses based on DUS findings in the context of recurrence have shed light on potential modifications to technique that may further improve the outcomes.

The short and medium term outcomes of EVTA are highly favourable when compared to conventional surgery in terms of both clinical efficacy and QoL parameters. Currently used EVLA techniques are safe, efficacious, expeditious, cost-effective and are now standing the test of time.

Overall, this thesis has given potential for the development of small, incremental advances that in themselves result in modest improvements but as a collective may result in progressive improvement in technique efficacy and patient outcomes. Future work should seek to add level 1 evidence to the preliminary work carried out in this thesis to optimize the techniques and further improve clinical success and patient experience

The EVTA procedures have often fallen under the populist banner of "minimally-invasive" surgery. Whilst there are certainly some short-term advantages over surgery in terms of reduced pain, quicker return to normal activity and preserved QoL, the primary treatment aim should not be minimal invasiveness but cure[430]. Data from this thesis suggest that the "invasiveness" of EVLA should be increased to both deliver higher energy at the SFJ to ensure flush occlusion, and treat all identifiable GSV reflux, in order to further reduce long-term clinical recurrence rates, which have been shown to negatively impact on clinical and QoL parameters. However, the patient impact of this "increased invasiveness" may be offset by other technique modifications such as buffering of tumescent anaesthesia, performing concomitant ambulatory phlebectomy rather than foam sclerotherapy of varicosities and using higher-wavelengh, lower-power laser.

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# Glossary

| | |
|---|---|
| AASV | Anterior Accessory Saphenous Vein |
| ASVAL | Ambulatory Selective Vein Ablation under Local anaesthesia: surgical technique of phlebectomy with truncal preservation |
| AUC | Area under the curve: statistical test |
| AVM | Arteriovenous malformation |
| AVVQ | Aberdeen Varicose Vein Questionnaire: a disease-specific quality of life instrument |
| BMI | Body Mass Index ($kgm^{-2}$) |
| CEAP | Clinical aEtiologic Anatomical Pathological scoring system for SVI |
| CFV | Common femoral vein |
| CHIVA | *cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatoire*: technique of surgical correction of SVI with preservation of GSV |
| CI | Confidence interval |
| CT | Computed Tomography |
| CVA | Cerebrovascular accident; "stroke" |
| CVI | Chronic Venous Insufficiency |
| CVD | Chronic Venous Disease |
| DUS | Duplex Ultrasound |
| DVI | Deep venous insufficiency |
| DVT | Deep vein thrombosis |
| EFE | Endovenous fluence equivalent ($Jcm^{-2}$) |
| EHIT | Endovenous heat-induced thrombosis |
| EQ5D | Euroqol 5-Domain utility index; generic quality of life instrument |
| EVAR | Endovascular aneurysm repair |
| EVLA | Endovenous laser ablation |
| EVTA | Endovenous thermal ablation |
| F-A | Friedman ANOVA: statistical test |
| FDA | Food and Drug Administration, USA |

| | |
|---|---|
| FET | Fisher's Exact Test: statistical test |
| g | gram: unit of weight (may be prefixed to denote different magnitudes) |
| GA | General anaesthetic |
| GSV | Great Saphenous Vein |
| HELP-1 | Hull Endovenous Laser Project – 1: RCT of EVLA versus HTSA for primary, symptomatic SFJ/GSV reflux |
| HHD | Hand-held doppler |
| HTA | Health technology assessment |
| HTSA | High-tie, stripping and avulsions; conventional surgical technique |
| ICAM | Intercellular adhesion molecule |
| IQR | Interquartile range |
| ITT | Intention to treat |
| IVC | Inferior vena cava |
| J | Joule: unit of energy |
| K-S | Kolmogorov-Smirnov test: statistical test of normality |
| l | litre: unit of volume (may be prefixed to denote different magnitudes) |
| LA | Local anaesthetic |
| LDS | Lipodermatosclerosis |
| LEED | Linear Endovenous Energy Density ($Jcm^{-1}$) |
| LMWH | Low molecular weight heparin |
| m | Metre: unit of length may be prefixed to denote different magnitudes |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MMP | Matrix metalloproteinase |
| MRI | Magnetic Resonance Imaging |
| MWU | Mann Whitney U Test: statistical test |
| $NaHCO_3$ | Sodium bicarbonate |
| NHS | National Health Service (UK) |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| OR | Odds Ratio |
| PE | Pulmonary embolism |
| PFO | Patent foramen ovale |

| | |
|---|---|
| PROMs | Patient-reported outcome measures |
| QALY | Quality-adjusted life year |
| QDS | Quarter die sumendus (4 times per day) |
| QoL | Health-related quality of life |
| R&D | Research and development |
| RCT | Randomised clinical trial |
| REC | Research ethics committee |
| REVAS | Recurrent varices after surgery |
| RFA | Radiofrequency ablation |
| ROC | Receiver operator characteristic |
| RR | Relative Risk |
| s | Second: unit of time |
| SD | Standard deviation |
| Seldinger technique: | Invented in 1952 by the Swedish radiologist Sven-Ivar Seldinger (1921-1998). Means of endovascular access and navigation using guidewires and sheaths. |
| SF36 | Short form 36-item generic quality of life instrument |
| SF6D | Short form 6-domain utility index; derived from SF36 |
| SFJ | Saphenofemoral junction |
| SMC | Smooth muscle cell |
| SPJ | Saphenopopliteal junction |
| SSV | Small saphenous vein |
| STD | Sodium tetradecylsulphate: sclerosing agent |
| SVI | Superficial venous insufficiency |
| SW | Shapiro-Wilk test: statistical test of normality |
| T-test | Student's t-test |
| TIMP | Tissue inhibitor of matrix metalloproteinase |
| TIPP | Trans-illuminated powered phlebectomy |
| TDS | Ter die sumendus (3 times per day) |
| TTO | Time Trade Off: method of QALY calculation |
| UGFS | Ultrasound-guided foam sclerotherapy |
| UK | United Kingdom |
| USA | United States of America |
| VAS | Visual Analogue Scale |
| VCAM | Vascular cell adhesion molecule |
| VCSS | Venous Clinical Severity Score |

| | |
|---|---|
| VEGF | Vascular endothelial growth factor |
| VTE | Venous Thromboembolism |
| W | Watt: unit of power |
| WSR | Wilcoxon Signed Rank test: statistical test |
| $\chi^2$ | Pearson's Chi-square test: statistical test |

# Appendix 1: Supplementary Figures for Study 1

**Figure S- 1 a-h: SF36 Domain Scores over time (Study 1)**

SF36 domain scores at baseline ("pre-op"), 1- and 2-years for Surgery and EVLA groups in Study 1.  There were no intergroup differences at any time point.

**Intragroup analysis**:
**Surgery group**: Equivalent 1- and 2-year domain scores (PF, p=0.945; R-P, p=0.634; BP, p=0.328; GH, p=0.445; Vit, p=0.418; SF, p=0.248; R-E, p=0.468).

**EVLA group**: There were no differences between 1 and 2-year scores for PF (p=0.074), R-P (p=0.175), SF (p=0.719) or R-E (p=0.792) domains, but 2-year scores for BP (p=0.028), GH (p=0.001), Vit (p=0.038) and MH (p=0.023) domains did deteriorate over 1 year.  However, the BP scores at 2 years remained significantly higher than baseline (p=0.001), with no differences between the same time-points for GH (p=0.667), Vit (p=0.246), or MH (p=0.607)



S- 1a: Physical Functioning



S- 1b: Role-physical
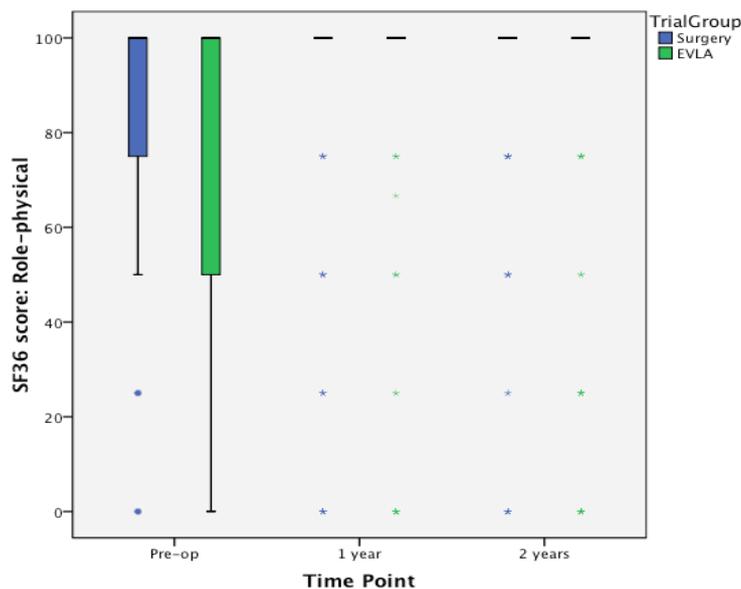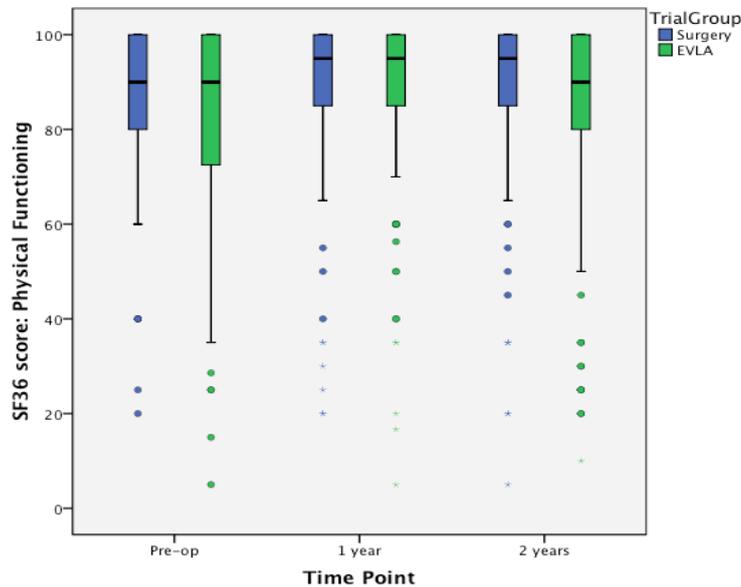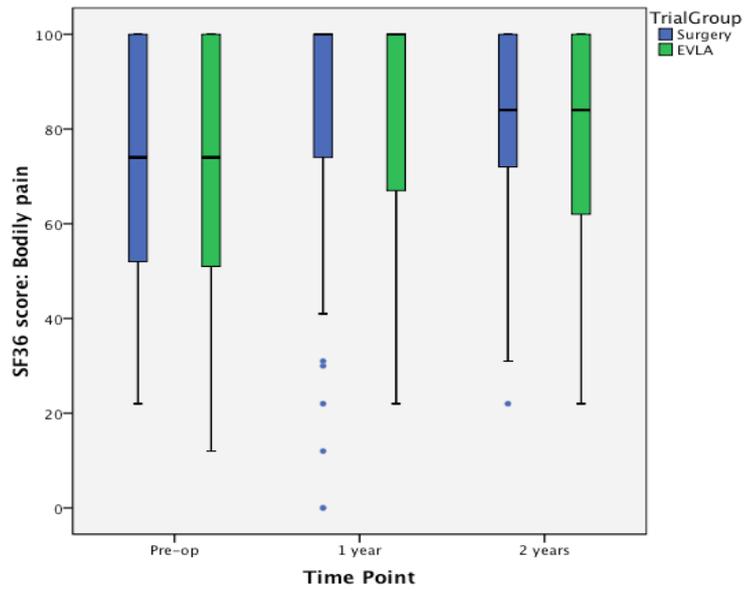
S- 1c: Bodily pain
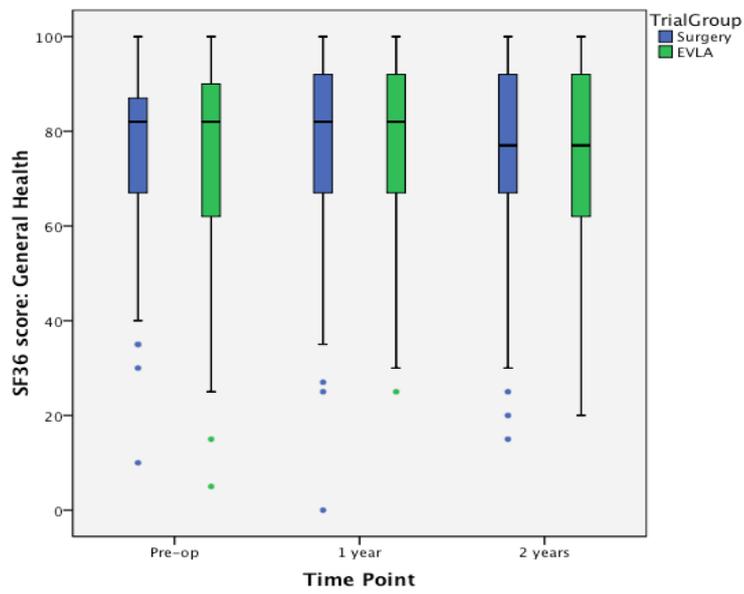


S- 1d: General Health
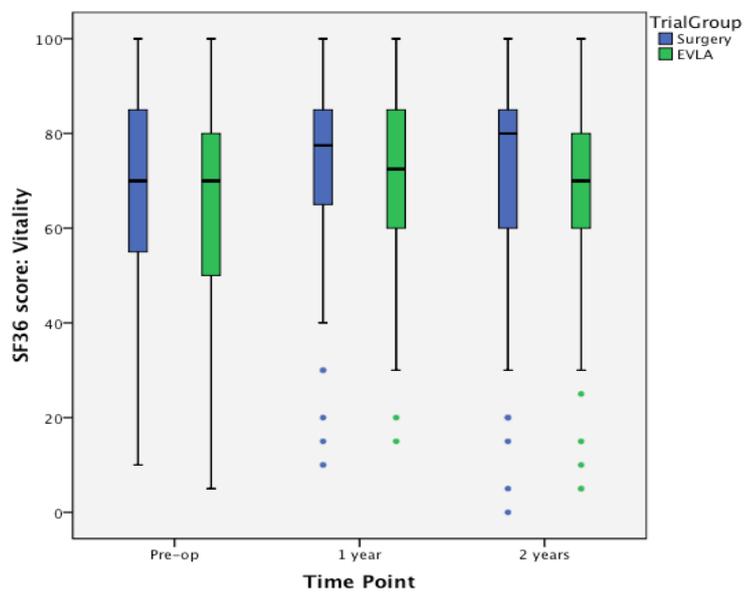


S- 1e: Vitality
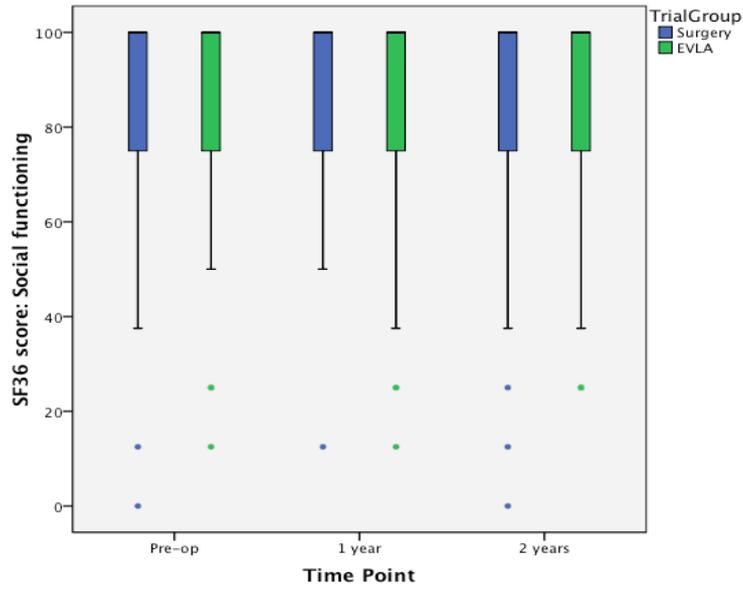
S- 1f: Social Functioning
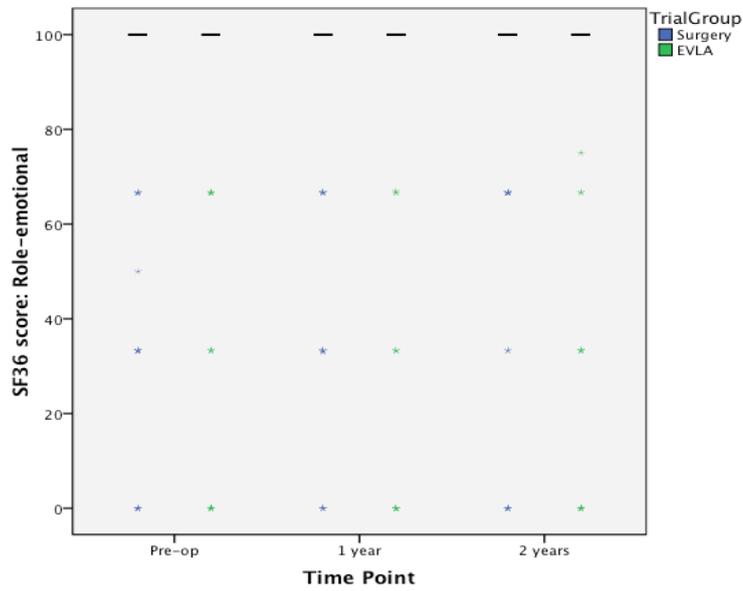


S- 1g: Role-emotional
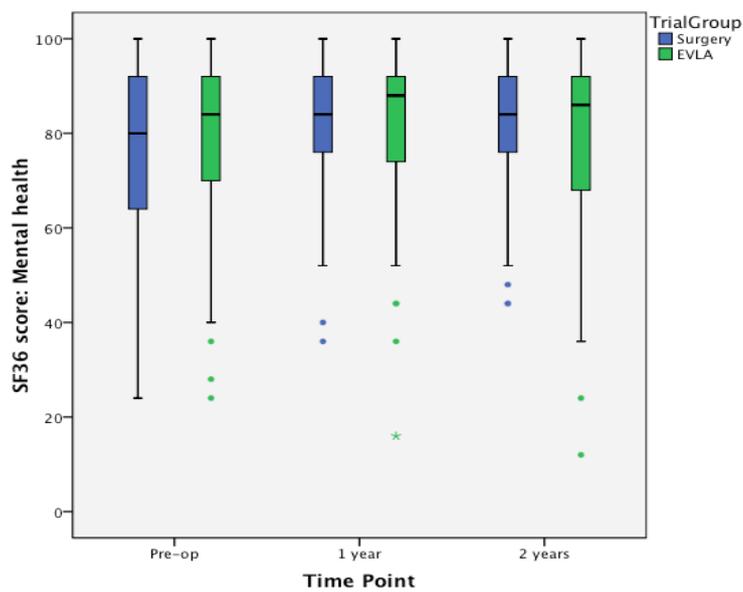


S- 1h: Mental Health

**Figure S- 2: SF36 Domain Scores at 2 years: Clinical Recurrence versus No Recurrence (Study 1)**

In a comparison of patients with and without clinical recurrence at up to 2 years, there were no differences in SF36 domain scores at 2-year follow-up.
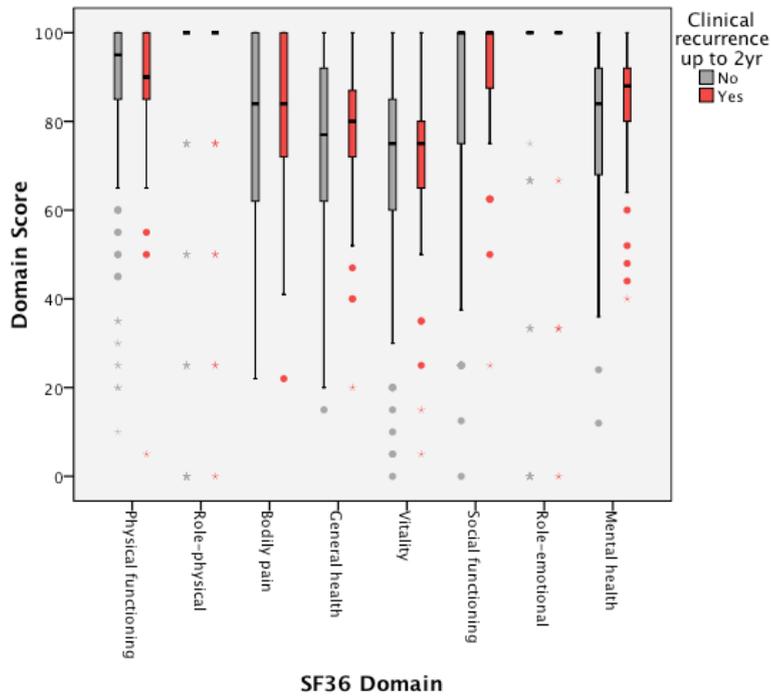


**Figure S- 3: EQ5D Utility Index Scores at 2 years: Clinical Recurrence versus No Recurrence (Study 1)**

There were no differences in EQ5D utility index scores between patients with and without evidence of clinical recurrence at two years.
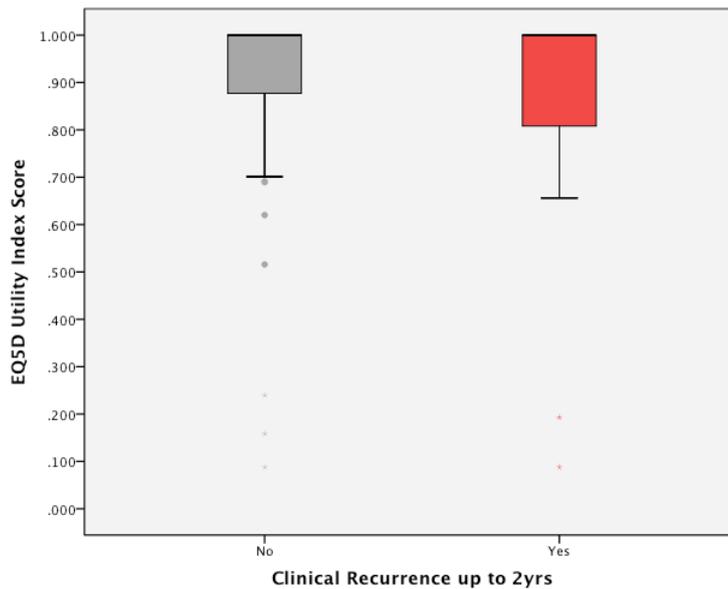
**Figure S- 4: SF36 Domain Scores at 2 years: Patients with Clinical Recurrence (Study 1)**

When comparing patients with clinical recurrence across treatment modalities, there were no differences at 2 years in any of the SF36 domain scores.
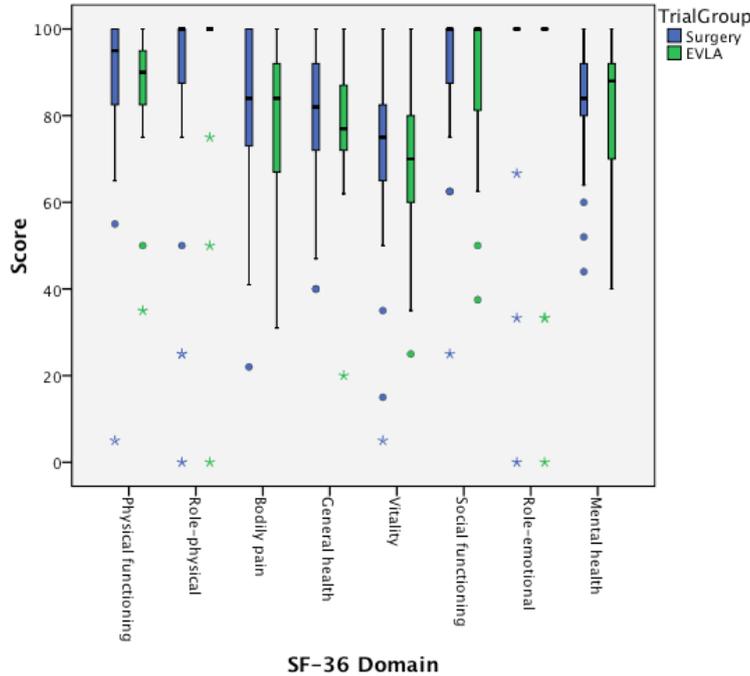


**Figure S- 5 a-h: SF36 Domain Scores - Patients with Clinical Recurrence (Study 1)**

In those patients with clinical recurrence in the Surgery group, there were no significant differences between baseline and 2-year scores for any of the SF36 domains, with the exception of an improvement in Mental Health (PF p=0.752; R-P p=0.322; BP p=0.074; GH p=0.558; Vit p=0.636; SF p=0.196; R-E p=0.157; MH p=0.002, Related-Samples WSR Test).

The EVLA patients with clinical recurrence demonstrated maintained improvements in Bodily pain, with no significant differences between baseline and 2-year scores for any of the other domains (PF p=0.832; R-P p=0.068; BP p=0.036; GH p=0.432; Vit p=0.527; SF p=0.480; R-E p=0.157; MH p=0.925, Related-Samples WSR Test)
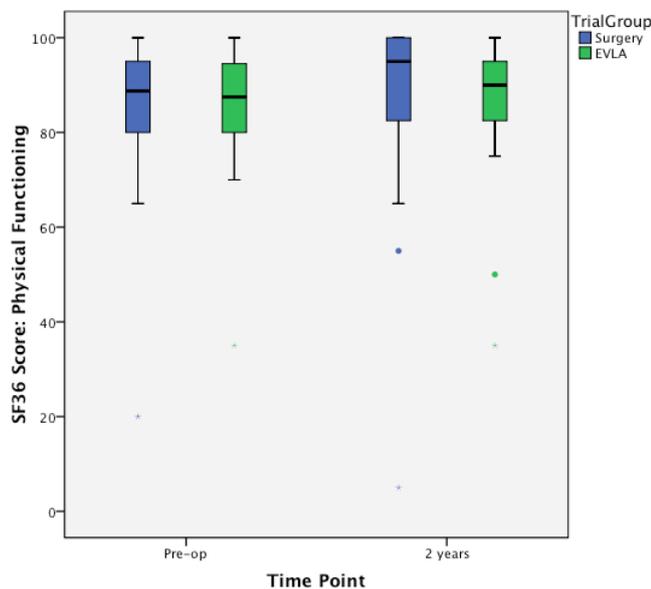


S- 5a: Physical Functioning
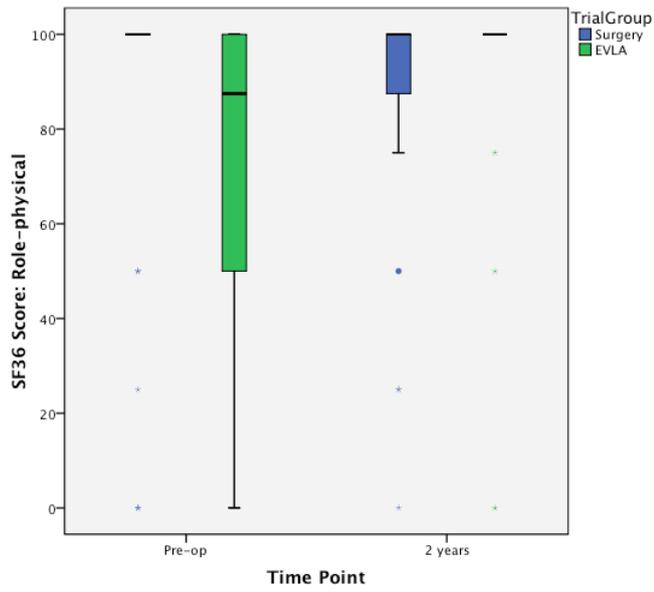
S- 5b: Role-physical
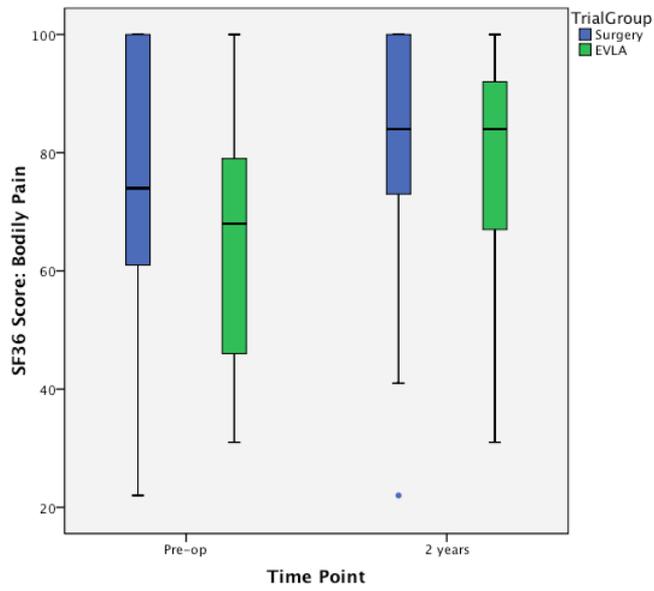


S- 5c: Bodily Pain
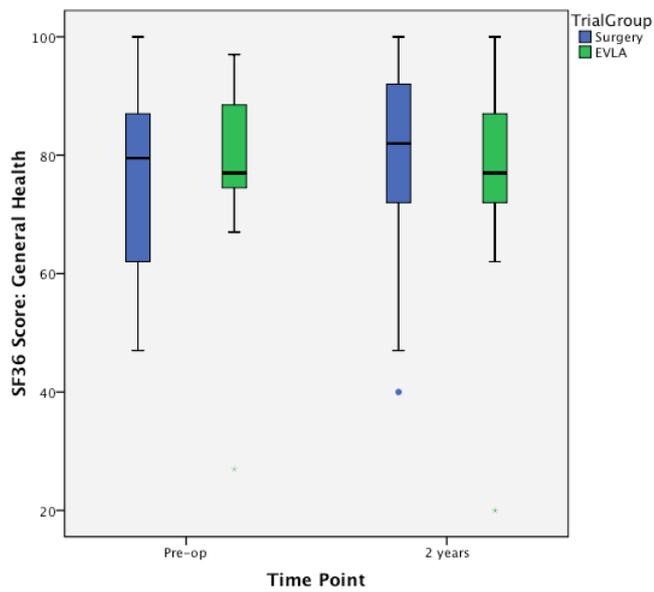


S- 5d: General Health

S- 5e: Vitality
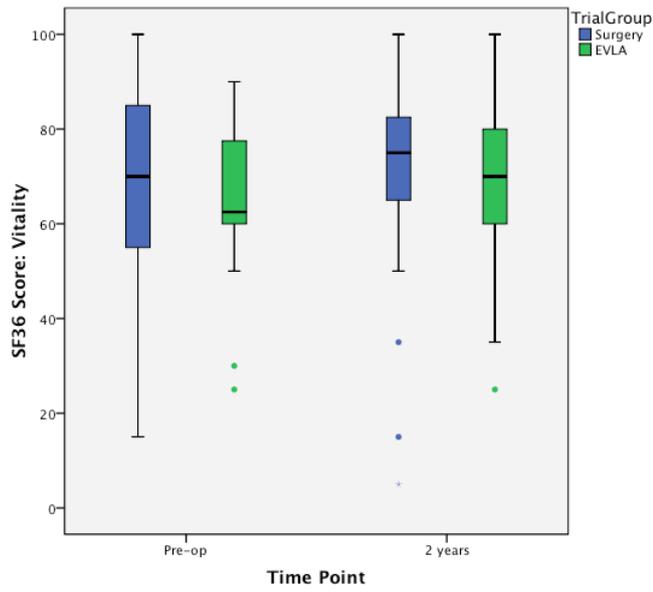
S- 5f: Social Functioning
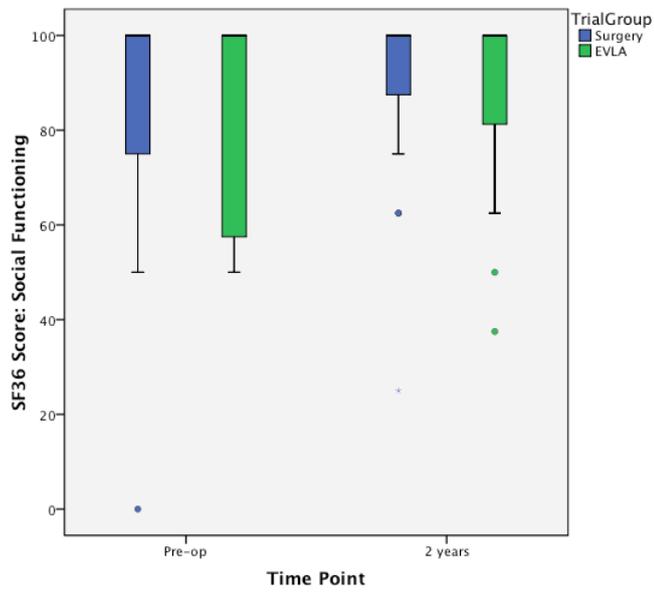
S- 5g: Role-emotional
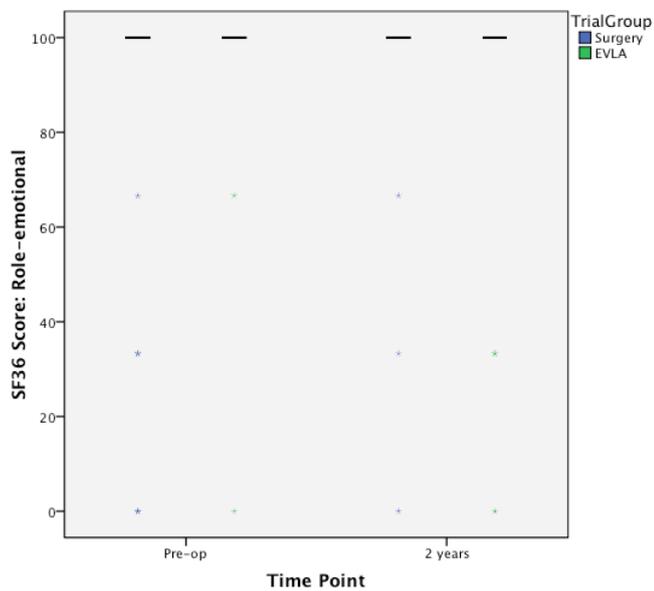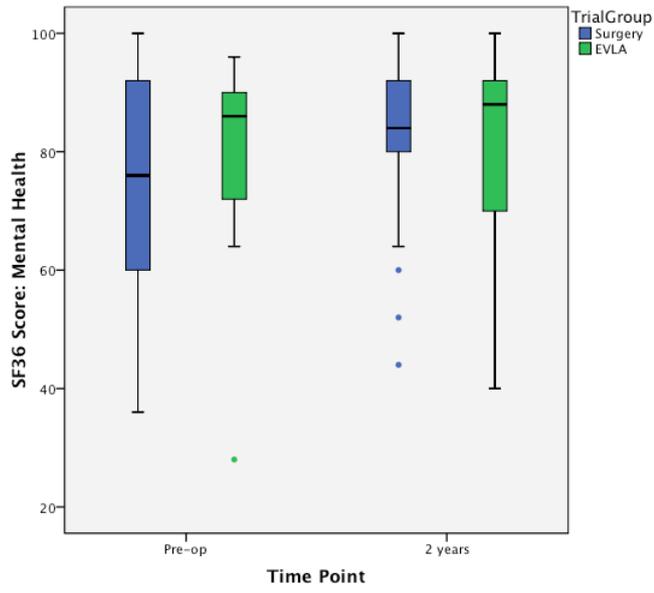
S- 5h: Mental Health

# Appendix 2: Supplementary Figures for Study 3

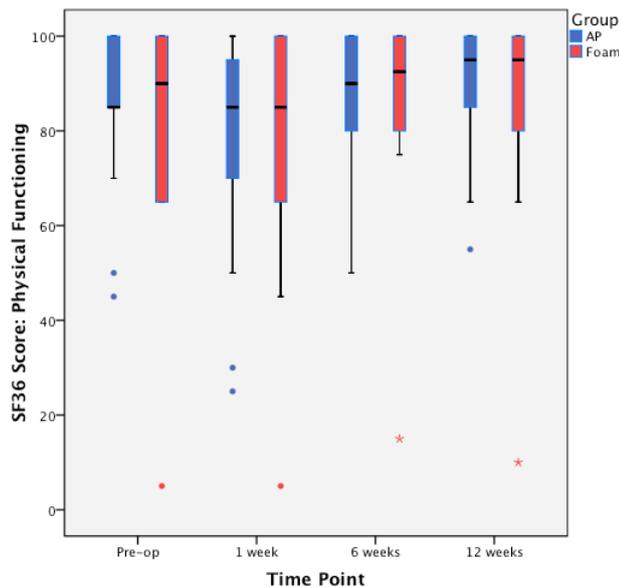**Figure S- 6 a-h: SF36 domain scores over time (Study 3)**

SF36 domain scores for the Unbuffered and Buffered groups from baseline to 12-week follow-up.  There were no significant intergroup differences with the exception of a marginally better Bodily pain score in the Unbuffered group at 6 weeks (p=0.034).

## Intragroup analysis
**Unbuffered group**: Significant deterioration in PF (p=0.038) and BP (p=0.004) from baseline to 1 week; no other differences between baseline and 1 week (R-P, p=0.472; GH, p=0.310; Vit, p=0.372; SF, p=0.605; R-E, p=0.470; MH, p=0.913).

At 6 weeks, no differences from baseline, with the exception of modest improvements in SF and MH (PF p=0.335; R-P p=0.325; BP p=0.096; GH p=0.221; Vit p=0.208; SF p=0.048; R-E p=0.143; MH p=0.043)

At 12 weeks, significantly improved BP (p=0.009) and R-P (p=0.05), with no further differences over baseline (PF p=0.161; GH (p=0.486); Vit p=0.749; SF p=0.058; R-E p=0.157; MH p=0.895).

**Buffered group:** No changes over baseline at 1 week, with the exception of a small decline in SF (PF p=0.330; R-P p=0.765; BP p=0.106; GH p=0.190; Vit p=0.828; SF p=0.036; R-E p=0.223; MH p=0.209).

At 6 weeks, significant improvements over baseline in PF (p=0.019), R-P (p=0.014), BP (p=0.023) and Vit (p=0.014).  Improvements in SF (p=0.054) approached statistical significance.  No differences from baseline in GH (p=0.099), R-E (p=0.301) or MH (p=0.181).

At 12 weeks, sustained significant improvements over baseline in PF (p=0.034), BP (p=0.013), GH (0.010), Vit (p=0.012) and MH (p=0.004). R-P (p=0.059), SF (p=0.916) and R-E (p=0.655) were not significantly different to baseline.

Friedman's ANOVA revealed QoL improvement over time was significant in PF (Unbuffered, p<0.001; Buffered, p=0.048), R-P (Unbuffered, p=0.046; Buffered, p=0.029); BP (Unbuffered, p<0.001; Buffered, p=0.035) and SF (Unbuffered, p=0.011; Buffered, p=0.010).
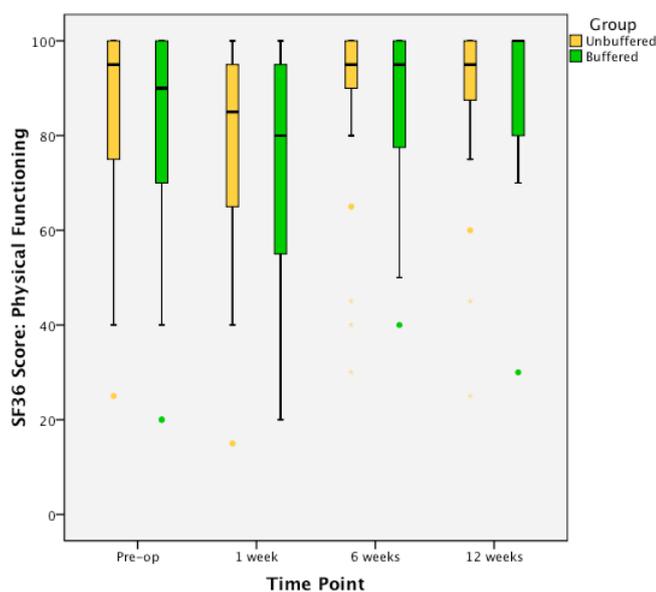


S- 6a: Physical Functioning
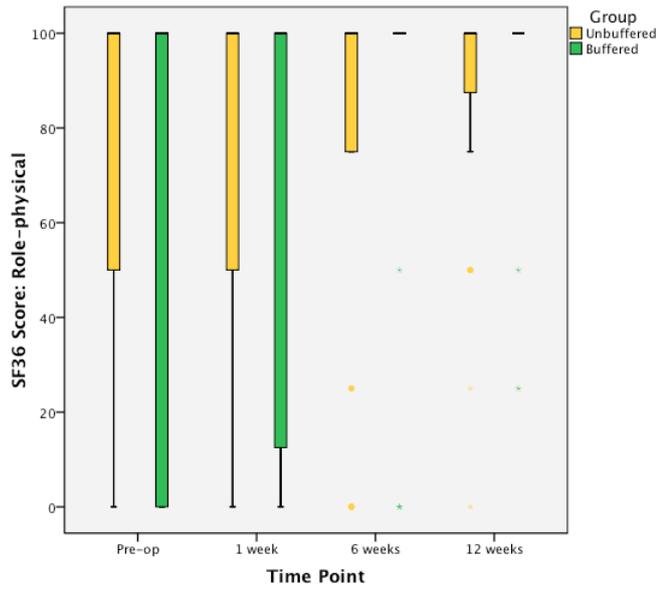
S- 6b: Role-physical
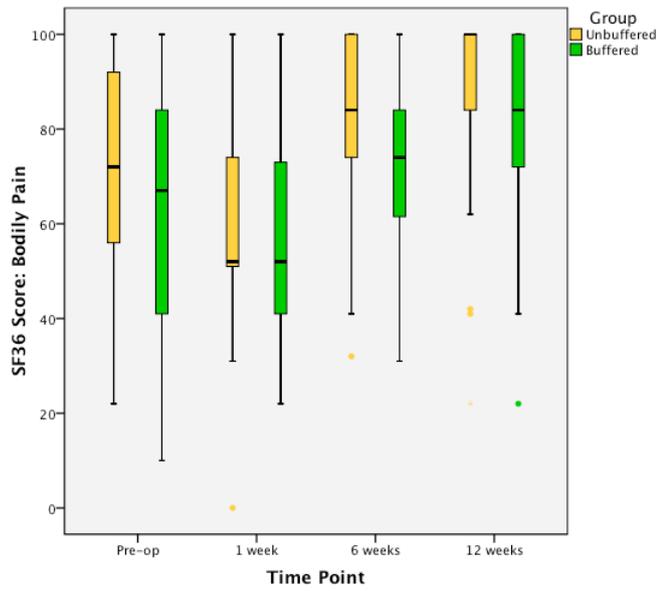


S- 6c: Bodily Pain
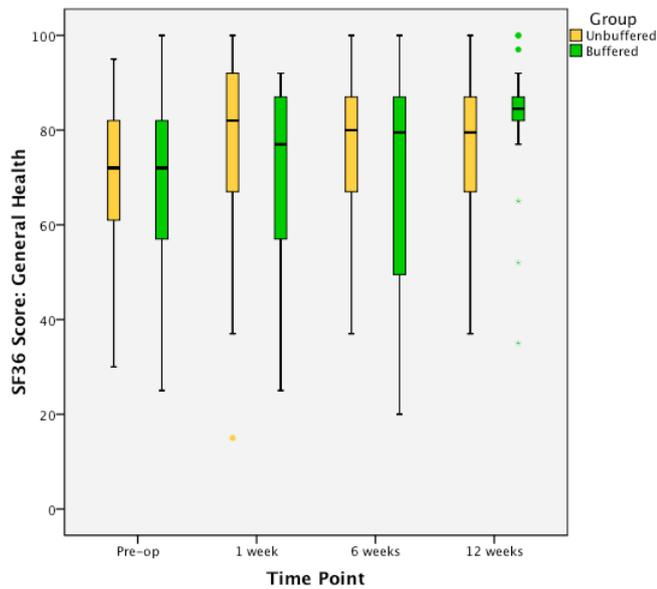


S- 6d: General Health
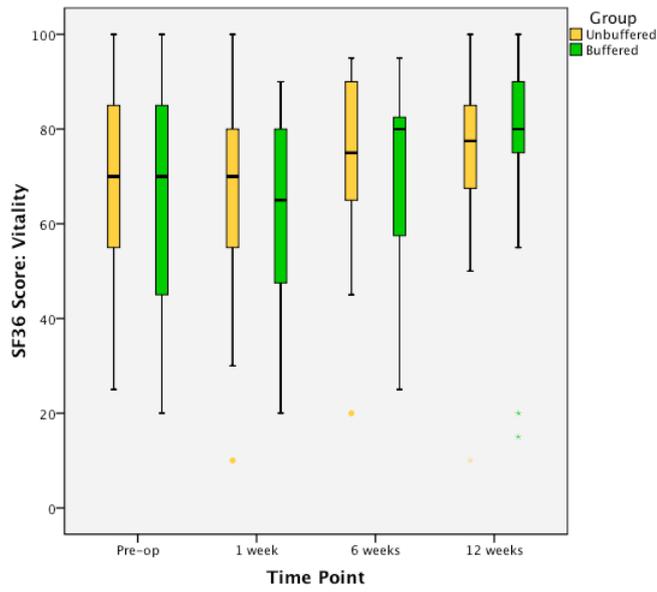
S- 6e: Vitality
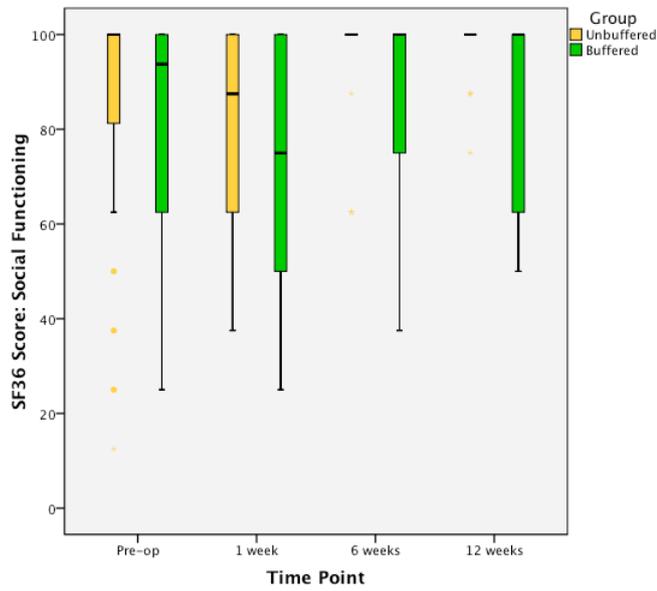


S- 6f: Social Functioning
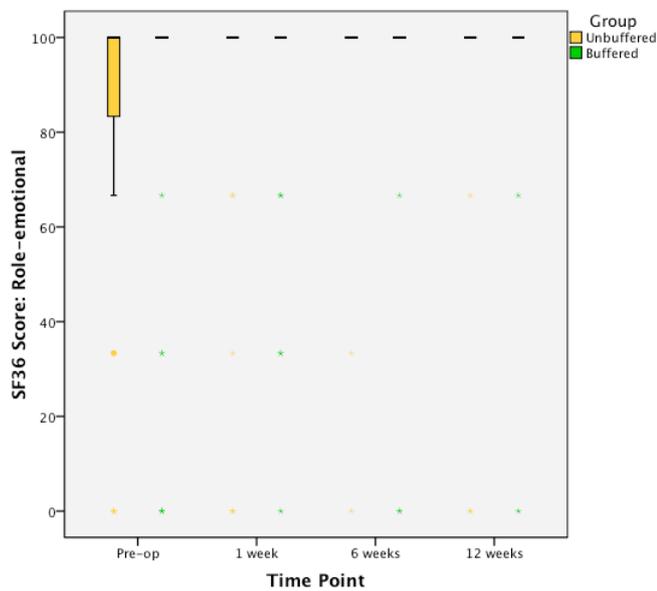


S- 6g: Role-emotional
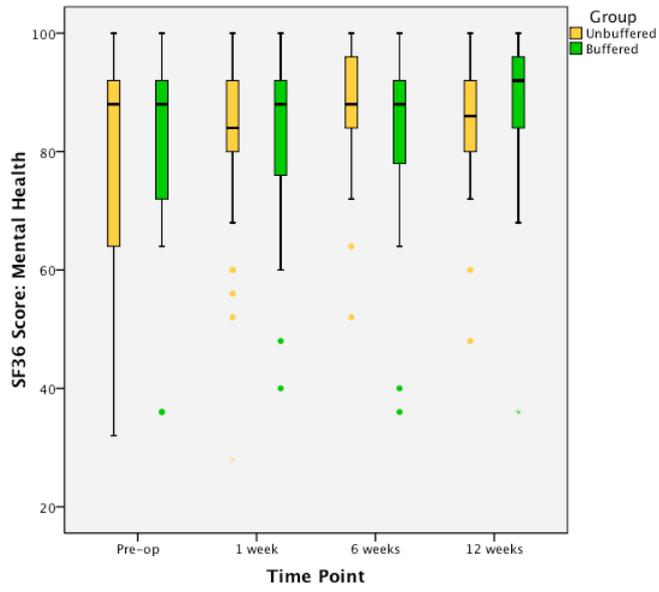
S- 6h: Mental Health

# Appendix 3: Supplementary Figures for Study 4

**Figure S- 7a-h: SF36 domain scores over time (Study 4)**

There were no intergroup differences at any time point

**Intragroup analysis**:
**AP group**: No differences from baseline scores for any domain at either 1- or 6-week follow-up (1 week - PF: p=0.809, R-P: p=0.180, BP: p=0.159, GH: p=0.163, Vit: p=0.454, SF: p=0.584, R-E: p=0.864, MH: p=0.583; 6-weeks - PF: p=0.754, R-P: p=0.720, BP: p=0.214, GH: p=0.585, Vit: p=0.110, SF: p=0.440, R-E: p=0.863, MH: p=0.434).

At 12 weeks, the AP group showed significant improvements over baseline scores for R-P (p=0.045), GH (p=0.005) and Vit (p=0.049).

**Foam group**: At 1 week, the Foam group displayed significant deterioration over baseline in the domain scores for PF (p=0.031) and BP (p=0.014). There were no differences from baseline for any domain score at 6 weeks (PF: p=0.263, R-P: p=0.785, BP: p=0.482, GH: p=0.112, Vit: p=0.739, SF: p=1.000, R-E: p=0.785, MH: p=0.527), or at 12 weeks (PF: p=0.058, R-P: p=0.785, BP: p=0.161, GH: p=0.139, Vit: p=0.797, SF: p=0.932, R-E: p=0.705, MH: p=0.944)



S- 7a: Physical Functioning
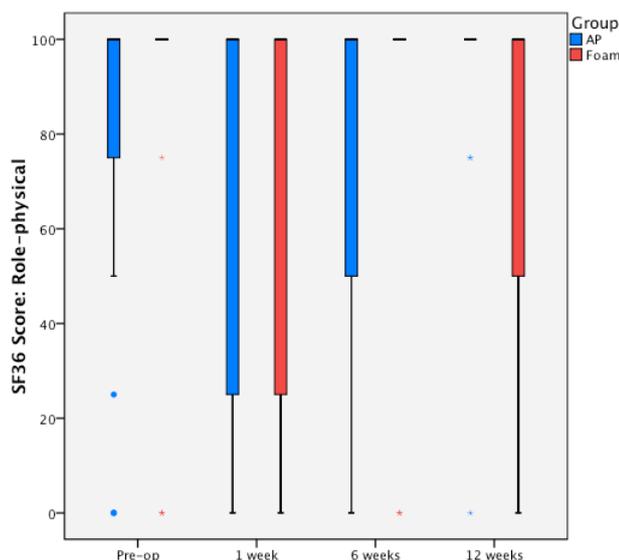


S- 7b: Role-physical

S- 7c: Bodily Pain
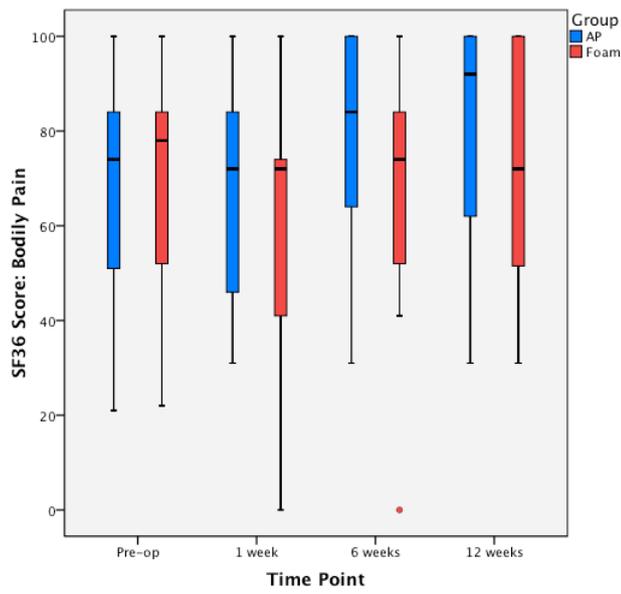


S- 7d: General Health
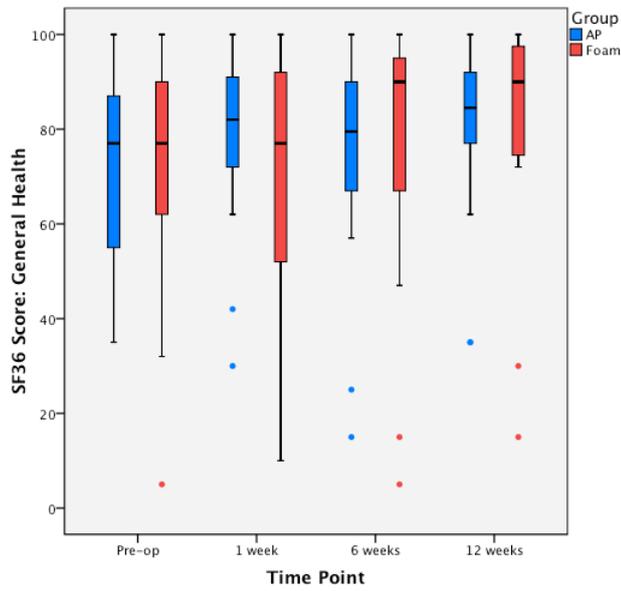


S- 7e: Vitality
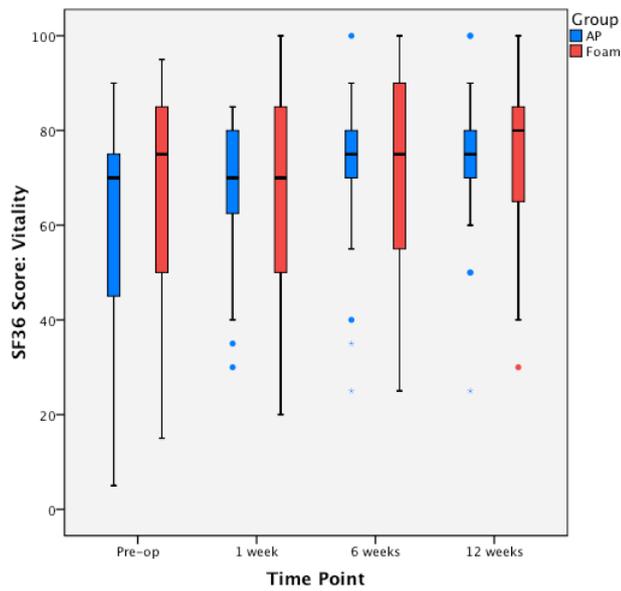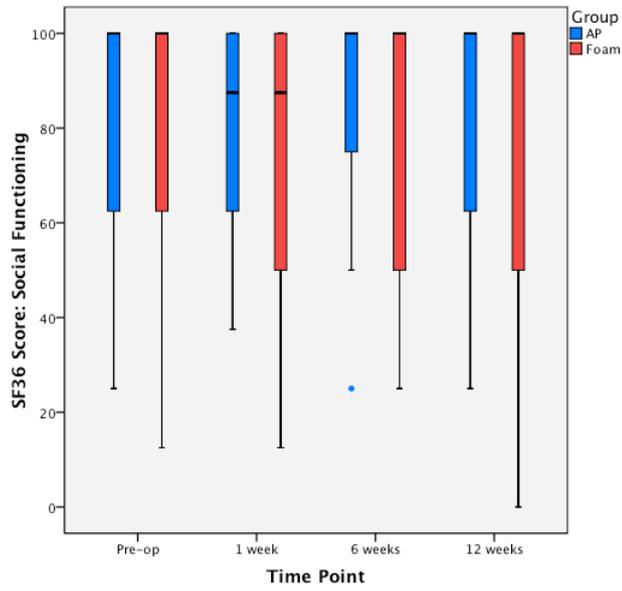
S- 7f: Social Functioning
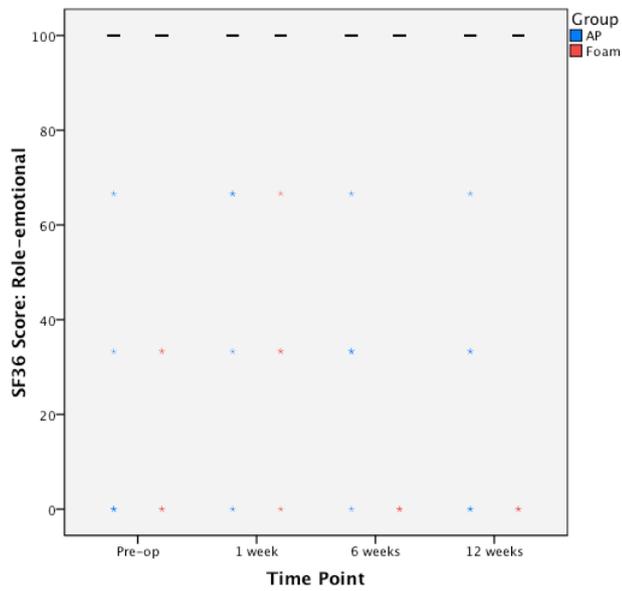


S- 7g: Role-emotional
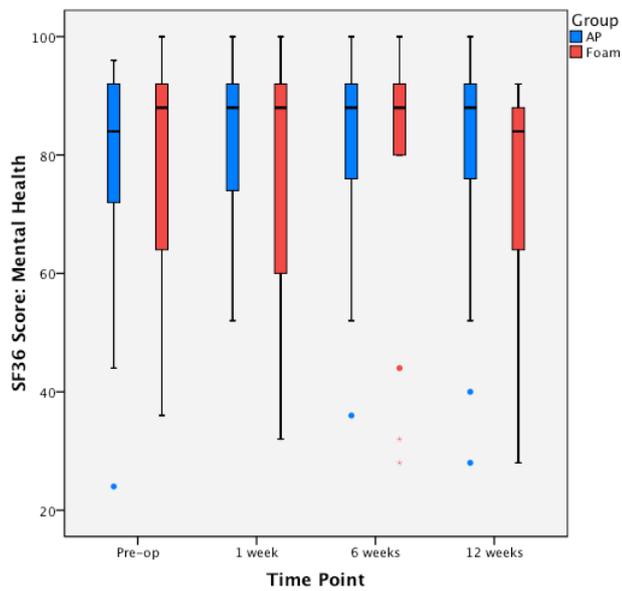


S- 7h: Mental Health

# Appendix 4: Supplementary Figures for Study 5

**Figure S- 8a-h: SF36 domain scores over time (Study 5)**

**Intergroup analysis**: Significantly better R-P domain scores at 1 week (p=0.046) in the 1470nm group compared to the 810nm group, but there were no other intergroup differences.

**Intragroup analysis:**
**810nm group:** Significant deterioration from baseline to 1 week in PF (p=0.047), R-P (p=0.040), BP (p=0.001) and SF (p=0.024).  No differences from baseline for any of the 6-week scores.  Significantly improved 12-week scores for BP (p=0.016) and GH (p=0.0440).

**1470nm group:** No changes from baseline to 1 week.  At 6 weeks, there were significant improvements over baseline for domain scores in R-P (p=0.043), GH (p=0.027) and SF (p=0.026). Improvements in PF (p=0.067), BP (p=0.051) and Vit (p=0.054) approached statistical significance.  There were sustained improvements over baseline in the 12-week scores for PF (p=0.035), BP (p=0.019), GH (0.016) and Vit (p=0.015).
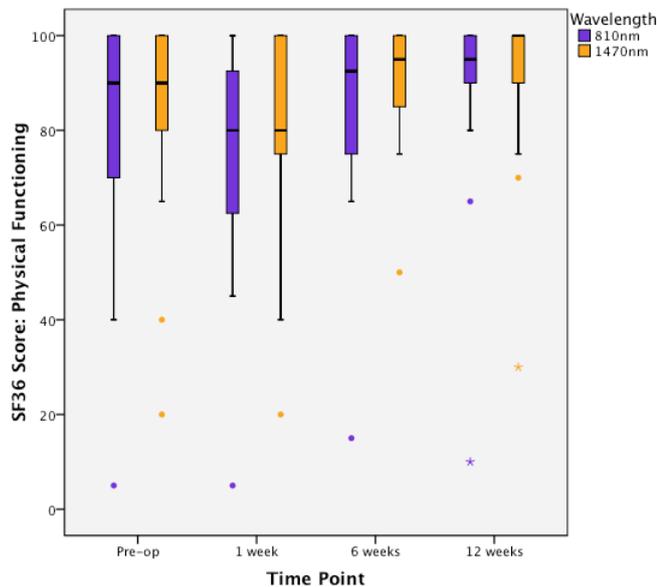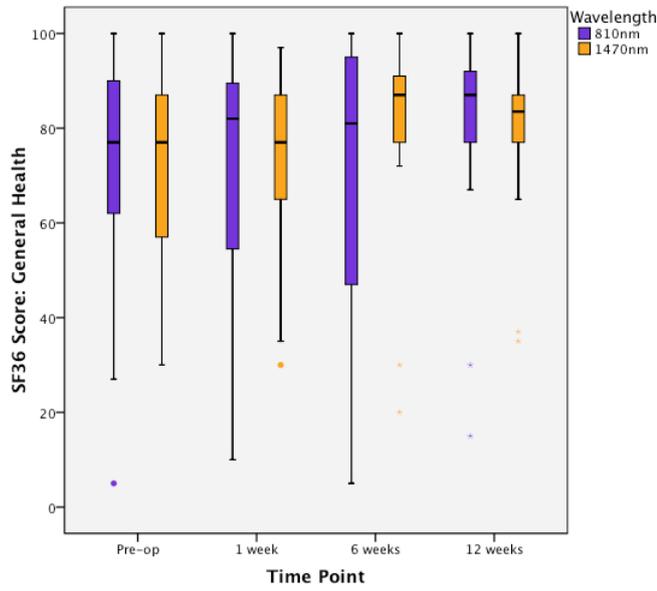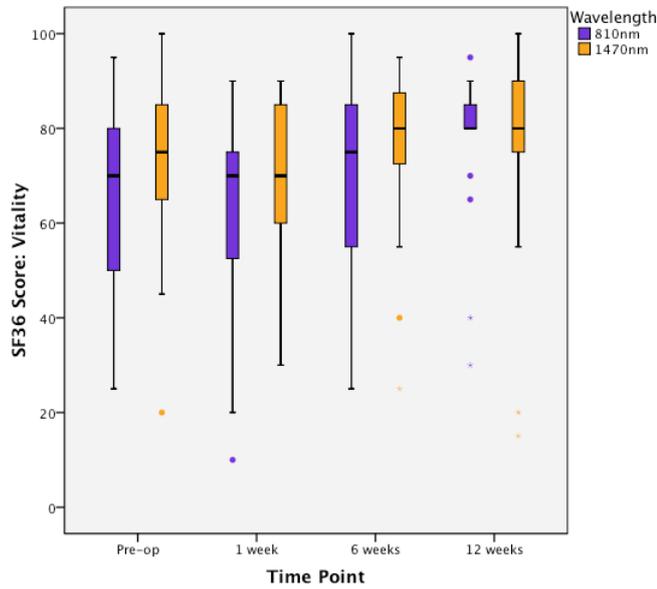


S- 8a: Physical Functioning
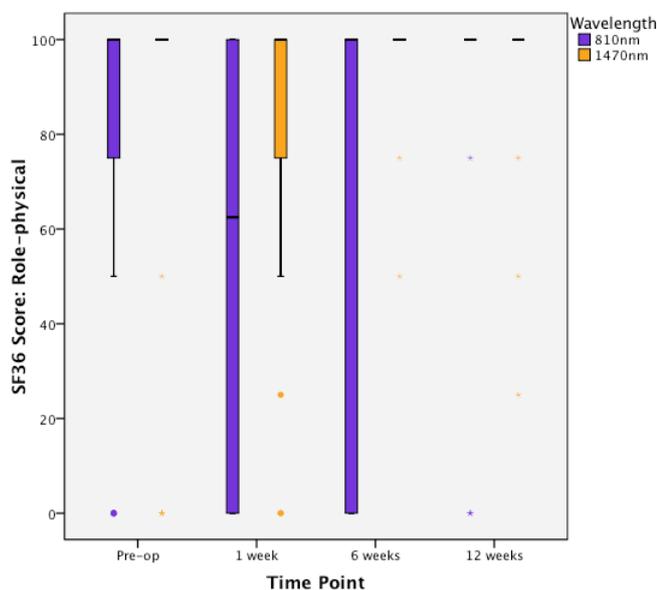


S- 8b: Role-physical
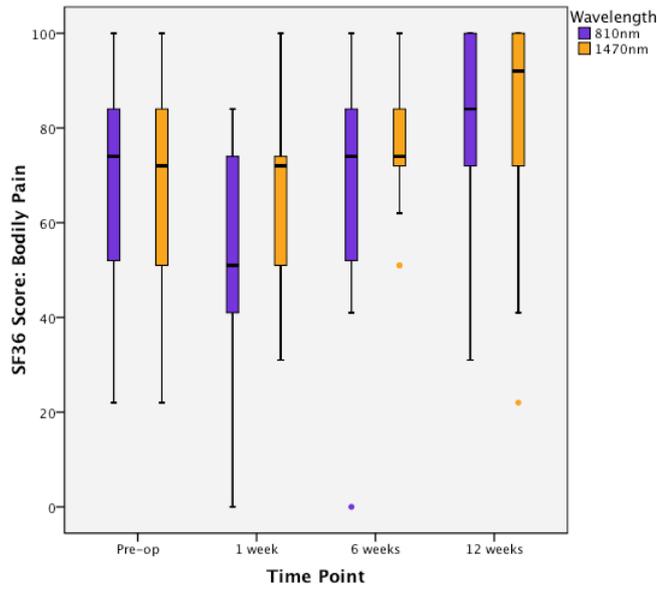
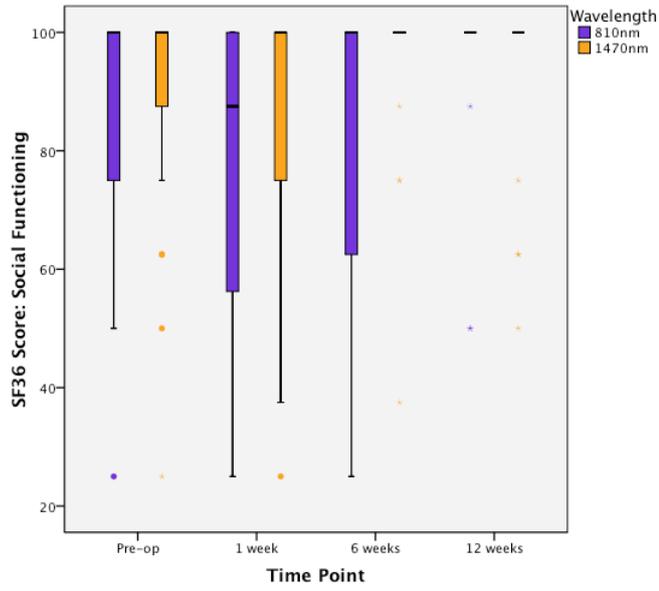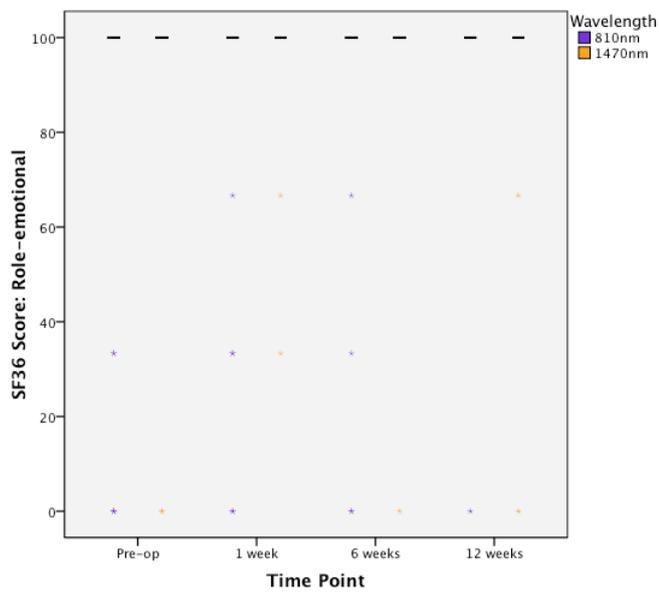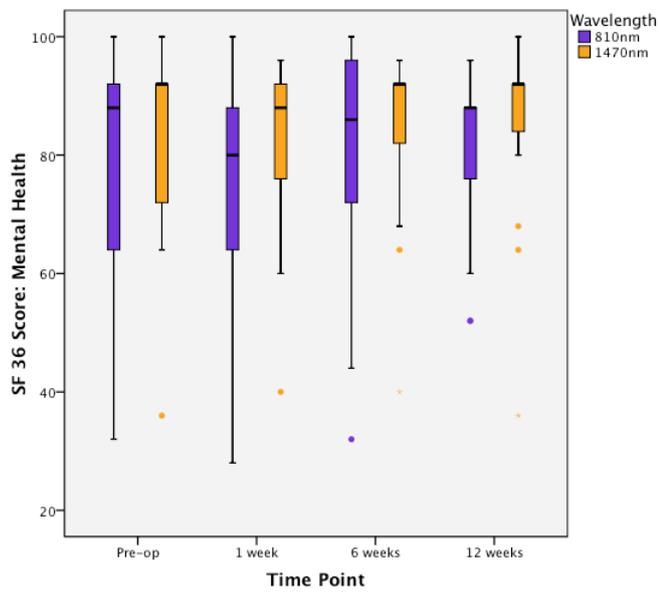S- 8c: Bodily Pain



S- 8d: General Health



S- 8e: Vitality

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S- 8f: Social Functioning



S- 8g: Role-emotional



S- 8h: Mental Health