Investigation of Femoropopliteal In Situ Valve Formation with the InterVene System

INFINITE-OUS

Version: CLN 003 Rev 04

03 November 2021

Sponsor
InterVene, Inc.
415 Grand Ave, Ste. 302
South San Francisco, CA 94080
USA

TABLE OF CONTENTS

PROTOCOL AGREEMENT

Investigation of Femoropopliteal In Situ Valve Formation with the InterVene System

Investigator Name

Investigational Site Name **Investigational Site Number**

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the device relating to past non-clinical and clinical experience, which were furnished to me by the Sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study.

I agree to keep records on all subject information (e.g., case report forms and informed consent statements), device shipments and return forms, and all other information collected during the study, in accordance with local and national regulations.

Investigator's Signature **Date**

CLINICAL STUDY SYNOPSIS

Protocol Number	CLN 003 Rev 04
Investigational Device	BlueLeaf® Endovenous Valve Formation System (BlueLeaf System)
Study Title	Investigation of Femoropopliteal In Situ Valve Formation with the InterVene System (INFINITE-OUS)
Sponsor	InterVene, Inc. 415 Grand Ave, Ste. 302 South San Francisco, CA 94080 USA
Study Purpose	To evaluate the safety and effectiveness of the BlueLeaf System for the restoration of deep venous competence for the treatment of symptomatic chronic venous insufficiency (CVI).
Study Population	Subjects with CVI and a Clinical Etiological Anatomical Pathophysiological (CEAP) classification of 3 – 6; up to 60 enrolled subjects
Investigational Sites	Up to 10 investigational sites outside the United States
Study Design	Prospective, non-randomized, multicenter pre-market feasibility study to evaluate subjects treated with the BlueLeaf System for the treatment of symptomatic CVI of the lower extremity.
Primary Endpoint	Primary Safety Endpoint: 1 Freedom from deep venous thrombosis (DVT) in the target vessel defined as: a. Thrombotic occlusion, or b. Stenosis due to thrombus accounting for > 50% diameter reduction through the 30-day follow-up; and/or 2 Freedom from symptomatic pulmonary embolism confirmed by contrast-enhanced pulmonary angiography through the 30-day follow-up. Primary Effectiveness Endpoint: Acute procedural success is evidence of hemodynamic effect as demonstrated by Intravascular ultrasound (IVUS) and/or venographic based evidence of pocket filling accompanied by leaflet or pocket mobility, at any autogenous valve sites. **NOTE:** 'Target vessel' is defined as the common femoral, proximal femoral, distal femoral and popliteal vein segments, in continuity (including duplications), of the treatment limb.
Inclusion Criteria	Subjects must meet the following criteria to be included in the study: 1. 18 years of age or older; 2. Symptomatic CVI subjects, CEAP classification 3 to 6;

	3. Failed at least 6 months of conservative therapy at some point during the course of their CVI management (symptoms not adequately resolved or patient non-compliant/unable to tolerate); 4. Willing and able to sign the approved informed consent form (ICF); 5. Willing to comply with follow-up evaluations and protocols; 6. Deep system venous reflux characterized by >1 second reflux time in two vein segments (vein segments defined as: proximal femoral, distal femoral, and popliteal), as assessed by duplex ultrasound (DUS) with patient in the standing position; 7. Presence of at least two potential target sites within the target vessel, which is defined as a segment within the femoral or popliteal vein that is: • not less than 7mm in luminal diameter, and • not more than 12mm in luminal diameter, and • is at least 3cm long (two target sites in a row must be spaced at least 1 cm apart), and • is absent severe obstructive features such as thrombus, synechiae, natural valves, major tributaries (valves can be formed opposite tributaries) or severe heterogeneous fibrotic changes of the vessel wall which, in the Investigator's opinion, would preclude formation of a valve, as preliminarily assessed by DUS, and then by IVUS, while the vein is under physiologically appropriate hemodynamic pressure, with IVUS being the definitive modality. 8. In the Investigator's opinion, the subject is a good candidate for treatment with the BlueLeaf System based on their symptoms, quality of life, anatomy, and the likelihood of benefit from continued conservative therapy.
Exclusion Criteria	Subjects with any of the following criteria are ineligible for inclusion in the study: 1. Untreated significant superficial venous incompetence which, in the opinion of the Investigator, may be the primary source of existing symptoms; 2. Deep venous intervention (includes stenting) in the target limb or outflow vessels within 3 months of consent; 3. Significant peripheral arterial disease with an ankle-brachial index of <0.70 or with incompressible vessels; 4. Contraindications to all protocol specified anticoagulation options; 5. Known and uncontrolled hypercoagulopathy (i.e. hypercoagulopathy that cannot be adequately managed/controlled with medication); 6. Acute deep venous thrombosis (DVT) within 6 months of consent; 7. Comorbidity risks or other concerns (e.g. recent cancer) which, in the opinion of the Investigator, limit longevity or likelihood of complying with the protocol and its prescribed follow up or would preclude the

	patient from open surgery in the event of a complication requiring surgical intervention (e.g. severe vein laceration); 8. General contraindications to local, regional or general anesthesia required for the index procedure; 9. NYHA Class III or IV heart failure; 10. Active systemic infection; 11. Women on long-term oral contraceptives; 12. Subject is enrolled in another clinical study that, in the opinion of the Investigator, may conflict with this study or compromise study results; 13. Invasive surgical procedure within the last 90 days that in the Investigator's opinion would interfere with the study procedure or results; 14. History of stroke within the last 6 months; 15. Subject is incarcerated or will be incarcerated during the course of the study; 16. Flow-limiting venous outflow obstruction central to the intended target sites, defined by a common femoral vein duplex exam found to have a continuous waveform without respiratory variation or a 50% or greater reduction in luminal cross–sectional area on IVUS; 17. Inadequate flow into or through the target vessel (Investigator's opinion); 18. Anatomy that does not support proper device access of the treatment vein through the ipsilateral common femoral or femoral vein; 19. Luminal diameter <7 mm between the vein access site and the intended treatment site, as assessed by IVUS, while the vein is under physiologically appropriate hemodynamic pressure; 20. A competent vein valve in any vein segment through which the device is likely to be inserted, as assessed by DUS (≤1 second reflux time) or with contrast venography (Investigator's opinion); 21. Chronic renal insufficiency with creatinine level of ≥2mg/dL; 22. Hemoglobin level <9.0 mg/dL; 23. Platelet count <50,000 or >1,000,000 per mm^3; 24. Total white blood cell count <3,000/mm^3; 25. Pregnant or lactating female; positive pregnancy test, women of childbearing potential must be tested; 26. Non-ambulatory patients; 27. Patients with a history of right heart failure occurring as a consequence of, for example, biventricular failure, intrinsic pulmonary disease, chronic thromboembolic pulmonary hypertension, and other etiologies that result in elevated right-sided pressures.
Follow-Up Schedule	Subjects will be followed through 360 days with annual visits through 5 years. (A total of 5 years of study participation.)

Medical Monitor	An independent Medical Monitor will review all primary safety endpoint events, unanticipated adverse device effects, and other important safety occurrences.
Data Safety Monitoring Board (DSMB)	An independent Data Safety Monitoring Board (DSMB) will review safety data from the study at predetermined time points as detailed in the protocol and as deemed necessary by the Sponsor or the DSMB Chair. The DSMB will make recommendations on protocol modifications and continuation of the study.
Core Laboratories	Assessment of duplex ultrasound, venography, IVUS, optional APG (Air Plethysmography) and ulcer photography will be performed by independent Core Laboratories.

1 INTRODUCTION AND BACKGROUND

Chronic venous insufficiency (CVI) with incompetence of the deep venous valves affects 20% of the adult population.[1] It has been estimated that varicose veins, the most common manifestation of CVI, are present in 25-33% of female and 10-20% of male adults.[2-9] The prevalence of CVI continues to rise as the population ages. Signs of CVI include edema, telangiectasia, reticular or varicose veins, and skin changes including ulceration.[10] Symptoms caused by CVI include chronic pain, edema, skin hyperpigmentation, dermatoliposclerosis, and ultimately ulceration in some patients (**Figure 1**). The symptoms of CVI are the source of significant patient discomfort, lost productivity and economic costs to society at large.[11-13]

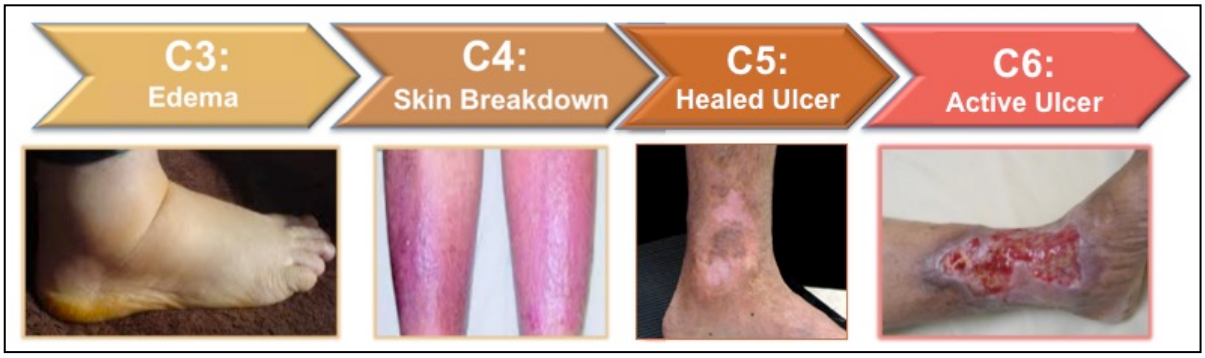


Figure 1. Stages of progression from edema to active ulceration in patients with chronic venous insufficiency.

The total cost of CVI is estimated to be approximately $1 billion in Germany, France, and the UK. Estimates of the total cost of CVI in the US exceed $ 1 billion.[14, 15] It is likely that these costs are much greater today, as these estimates are from the 1990's.

1.1 Pathophysiology of Chronic Venous Insufficiency

It is quite rare for CVI to result from congenital malformations.[10] The most frequent causes of CVI are from primary abnormalities of the venous wall and vein valves, or secondary changes resulting from previous venous thrombosis.[10] For many patients suffering from primary or secondary CVI, these painful symptoms are caused by failed venous valves in the legs (**Figure 2**).

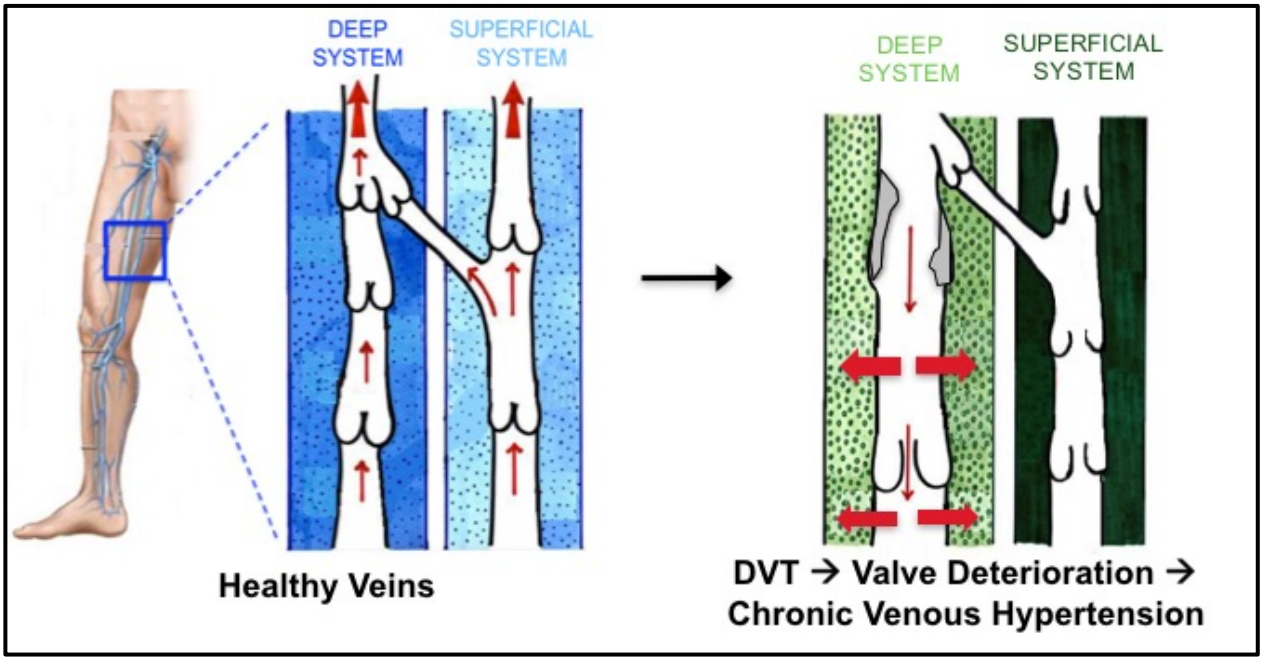


Figure 2. Healthy and diseased veins in the human lower extremity with reversal of flow in the superficial and deep venous systems.

When venous valves fail and blood is permitted to flow retrograde toward the feet (venous reflux), patients suffer from elevated venous pressures, which triggers an inflammatory cascade that leads to the edema, skin changes and ulceration previously described. In some cases, these changes in skin result from severe impairment of blood capillary circulation in the limbs of patients with CVI.[16] While many patients develop symptoms due to diseased superficial veins, a significant number of patients suffer from severe venous symptoms due to incompetent venous valves in the deep vein system. Unfortunately, deep system valve failure currently results in lifelong, often incapacitating symptoms of leg edema, pain, difficulty walking, and psychological disorders that are exacerbated by a lack of definitive treatment options. The standard of care is palliative and includes compression therapy, leg elevation and regular wound care. Studies have shown that patients with chronic venous ulcers suffer a reduced quality of life similar to that of patients with malignancies, diabetes and congestive heart failure.[12]

Various diagnostic measures have been used to identify the nature and extent of CVI. These measures are particularly valuable in light of the fact that the history and physical examination does not always accurately indicate the nature and extent of the underlying abnormality such as the anatomic extent, pathology, and cause.[17-19] For this reason, it will be important to utilize multiple diagnostic and measurement modalities in this study to gain a more complete picture of a patient's baseline disease state and to assess that patient's improvement following a procedure. In the past, localizing venous obstruction required a phlebogram but that is no longer the case thanks to advances in duplex scanning, which is considered simpler and more accurate than venography.[10] That said, ascending venography has maintained a role in demonstrating vein patency, defining anatomy, and distinguishing between primary and secondary disease. Ascending venography also plays a secondary role in detection of incompetent perforating veins.[10]

Descending venography is used to identify reflux (in the superficial or deep veins) and determine points of reflux from the pelvis to lower limbs and deep to superficial veins.[10] Other methods used to obtain information relating to morphology include varicography and liquid crystal thermography, amongst others. A variety of techniques, including ambulatory venous pressure, arm/foot pressure differential, air plethysmography and others, are available to gather hemodynamic information.[10]

1.2 Clinical Need

CVI patients with extensive deep vein reflux who fail superficial therapy are numerous and suffer from poor quality of life. The costs associated with palliative care is large, particularly if ulceration develops. The average direct cost of patients with venous ulcers has been estimated to be $15,700 over a median follow-up of one year, and this number is significantly higher for patients with untreatable disease and nonhealing ulcers.[20] Interventional options for patients suffering from extensive deep vein reflux are limited, with only a few centers offering a few varieties of technically-challenging open surgical procedures. This leaves most patients with nothing but the burdensome palliative care options previously described, or costly wound care management if the disease progresses. A less invasive, and easy to perform deep vein valve intervention is sorely needed for this patient population.

1.3 Treatment Strategies for Venous Valvular Incompetence

Open surgical and, more recently, minimally invasive techniques have been used to restore valve competence in the deep veins.[13, 21] Minimally invasive techniques have historically focused on valve implantation with a foreign body, but no clinically viable technologies have been proven out to date.[22] Unfortunately, open surgical techniques are invasive and can be technically challenging. For these reasons, open surgical venous procedures are performed in only a handful of highly specialized centers. However, their results support the hypothesis that restoration toward normal venous valve function in only one or two locations, without a significant foreign body implant, can relieve the symptoms of CVI. This observation is the basis of InterVene's approach. The BlueLeaf System is designed to mirror the goals of open surgical valve formation, but with a less invasive, percutaneous procedure. The goal of the BlueLeaf System is to percutaneously form one or more functional, autogenous deep venous valves and restore venous competence. An autogenous valve will henceforth be defined as a non-natural, newly formed valve that is either monocuspid (one autogenous leaflet) or bicuspid (two autogenous leaflets at the same vein level). Refer to the Investigator's Brochure (IB) for additional background information.

2 INTENDED USE AND DESCRIPTION OF THE STUDY DEVICE

2.1 Intended Use of the System

The BlueLeaf System is designed to treat patients with symptomatic CVI with evidence of deep venous valvular incompetence in the femoral and popliteal veins. The device is intended to form autogenous tissue leaflets from vein walls without the use of a permanent vascular implant.

2.2 Device Description

The BlueLeaf System is a single-use, disposable device used to modify the vein wall to form functional autogenous tissue valves that limit venous incompetence (**Figure 3)**. The device is supplied as a single, integrated system, but can be conceptually divided into 4 sub-components (**Figure 4**). The system is single-use, disposable, and provided in sterile form.

The BlueLeaf System enables a physician to access the vein to be treated through the groin area and advance the working end of the catheter to a treatment site, which is determined by a combination of fluoroscopic and intravascular ultrasound (IVUS) imaging modalities. Once the site has been accessed, the operator will use the device to carefully form one or more autogenous tissue valves out of the inner layers of the vein wall. Once completed, the device is withdrawn and the point of entry sealed.

The BlueLeaf System will be used only by qualified operators. For complete instructions, refer to the manufacturer's Instructions for Use (IFU). A current IFU will be provided with each BlueLeaf Catheter System. For additional device design and testing information, refer to the IB.

2.3 Device Traceability

Lot numbers will be used to trace devices used in the study.

3 PRIOR INVESTIGATIONS

The first generation InterVene device was evaluated in two patients in New Zealand in a First-in-Human experience (described in the IB). The first-generation device was a larger-bore system (20Fr), and utilized a distinct approach for valve formation, with separate tools for valve pocket formation and intimal incision.

This study is being performed to allow the Sponsor to collect safety and effectiveness on its BlueLeaf System in preparation for a larger Feasibility and/or Pivotal study.

4 STUDY OBJECTIVES

4.1 Study Purpose

The purpose of this study is to provide information on the BlueLeaf System for the formation of one or more autogenous vein valves constructed from autogenous leaflets in the femoral and/or popliteal vein, in subjects with CVI and who meet the specified eligibility criteria. In particular, the safety and technical feasibility of the procedure will be validated in humans, including the procedural steps, operator technique, and subject characteristics. The study will assess the safety and effectiveness of the study device acutely and through 5 years.

In addition, the study will capture information on the femoral and popliteal vein anatomic and physiologic characteristics before and after formation of the autogenous valves, with respect to imaging data from venography, IVUS and duplex ultrasound, and hemodynamic data generated from duplex ultrasound and quantitative air plethysmography (APG) (optional testing). This data will be used to determine the most appropriate imaging and physiologic measures for subsequent investigations. In addition, the study will assess changes in general patient reported outcome surveys such as SF-36, and venous quality of life indices including the rVCSS and VEINS-QOL/Sym as they relate to the study procedure.

4.2 Scope and Duration of the Study

The study commenced enrollment in November of 2017. Enrollment is expected to conclude 24 months later and subjects will be followed for 5 years after treatment.

Up to 10 investigational sites Outside the United States (OUS) will enroll up to 60 subjects, with expectation that approximately 30 of those 60 subjects will meet all inclusion/exclusion criteria and be eligible for the study treatment.

The study will provide initial insights into the following aspects of the study device and procedure:

- whether the device can be successfully delivered to the intended locations in the target vessel;

- technical challenges with use of study device;
- human factors related to the device and comprehension of the procedural steps;
- clinical safety of the device-specific aspects of the autogenous valve formation procedure;
- whether the device performs its intended purpose of forming functional autogenous valves that are durable over early (30-day) and long-term follow-up;
- characterization of device failures and analysis of their causes;
- anatomic and other patient-related characteristics that may impact device performance;
- therapeutic parameters that may impact device use, including sizes and actuation scheme of the device components.

4.3 Iterative Evaluation Process for Device, Procedure, Protocol Modifications

The study will have periodic subject outcome assessments and analyses by the Data Safety Monitoring Board (DSMB) in addition to a review by the Sponsor. The DSMB met after 7-day follow-up data was complete on the first three subjects prior to continued enrollment. Subsequent DSMB assessments will occur if/when there are substantial changes to the device or procedure which could impact subject safety. In this case, the DSMB will review the 7-day follow-up data of the first 3 subjects enrolled with the modified device.

Additionally, the DSMB will remain apprised of data as it comes in and a formal review will take place at least every 3 months during enrollment and during the first year of all subject's study follow-up.

5 CLINICAL STUDY DESIGN

This Study of the BlueLeaf System (INFINITE-OUS) is an interventional, non-randomized, multicenter, pre-market, single-arm prospective clinical trial. The analyses are descriptive in nature, with no planned statistical comparisons. The study is not hypothesis-driven and no formal hypotheses will be tested. For this reason, there is no sample size calculation but the total sample size is pre-specified at 30 treated subjects with data analyzed in an iterative fashion.

5.1 Study Population

The study population will include up to 30 male and female subjects treated with symptomatic, non-obstructive dominant, CVI who are candidates for lower extremity endovascular venous intervention to address incompetence of the femoropopliteal valves.

5.2 Inclusion Criteria

Subjects must meet the following criteria to be included in the study.

1. 18 years of age or older;
2. Symptomatic CVI subjects, Clinical Etiological Anatomical Pathophysiological (CEAP) classification 3 to 6;
3. Failed at least 6 months of conservative therapy at some point during the course of their CVI management (symptoms not adequately resolved or patient non-compliant/unable to tolerate);
4. Willing and able to sign the approved informed consent form (ICF);

5. Willing to comply with follow-up evaluations and protocols;
6. Deep system venous reflux characterized by >1 second reflux time in two vein segments (vein segments defined as: proximal femoral, distal femoral, and popliteal), as assessed by DUS with patient in the standing position;
7. Presence of at least two potential target sites within the target vessel, which is defined as a segment within the femoral or popliteal vein that is:
    - not less than 7mm in luminal diameter, and
    - not more than 12mm in luminal diameter, and
    - is at least 3cm long (two target sites in a row must be spaced at least 1cm apart), and
    - is absent severe obstructive features such as thrombus, synechiae, natural valves, major tributaries (valves can be formed opposite tributaries) or severe heterogeneous fibrotic changes of the vessel wall which, in the Investigator's opinion, would preclude formation of a valve,
8. as preliminary assessed by DUS, and then by IVUS, while the vein is under physiologically appropriate hemodynamic pressure, with IVUS being the definitive modality.
9. In the Investigator's opinion, the subject is a good candidate for treatment with the BlueLeaf System based on their symptoms, quality of life, anatomy, and the likelihood of benefit from continued conservative therapy.

5.3 Exclusion Criteria

Subjects with any of the following criteria are ineligible for inclusion in the study:

1. Untreated significant superficial venous incompetence which, in the opinion of the Investigator, may be the primary source of existing symptoms;
2. Deep venous intervention (includes stenting) in the target limb or outflow vessels within 3 months of consent;
3. Significant peripheral arterial disease with an ankle-brachial index of <0.70 or with incompressible vessels;
4. Contraindications to all protocol specified anticoagulation options;
5. Known and uncontrolled hypercoagulopathy (i.e. hypercoagulopathy that cannot be adequately managed/controlled with medication);
6. Acute deep venous thrombosis (DVT) within 6 months of consent;
7. Comorbidity risks or other concerns (e.g. recent cancer) which, in the opinion of the Investigator, limit longevity or likelihood of complying with the protocol and its prescribed follow up or would preclude the patient from open surgery in the event of a complication requiring surgical intervention (e.g. severe vein laceration);

8. General contraindications to local, regional or general anesthesia required for the index procedure;
9. NYHA Class III or IV heart failure;
10. Active systemic infection;
11. Women on long-term oral contraceptives;
12. Subject is enrolled in another clinical study that, in the opinion of the Investigator, may conflict with this study or compromise study results;
13. Invasive surgical procedure within the last 90 days that in the Investigator's opinion would interfere with the study procedure or results;
14. History of stroke within the last 6 months;
15. Subject is incarcerated or will be incarcerated during the course of the study;
16. Flow-limiting venous outflow obstruction central to the intended target sites, defined by a common femoral vein duplex exam found to have a continuous waveform without respiratory variation, or a 50% or greater reduction in luminal cross–sectional area on IVUS;
17. Inadequate flow into or through the target verssel (Investigator's opinion);
18. Anatomy that does not support proper device access of the treatment vein through the ipsilateral common femoral or femoral vein;
19. Luminal diameter <7 mm between the vein access site and the intended treatment site, as assessed by IVUS, while the vein is under physiologically appropriate hemodynamic pressure;
20. procedure competent vein valve in any vein segment through which the device is likely to be inserted, as assessed by DUS (<1 second reflux time) or with contract venography (Investigator's opinion);
21. Chronic renal insufficiency with creatinine level of ≥2mg/dL;
22. Hemoglobin level <9.0 mg/dL;
23. Platelet count <50,000 or >1,000,000 per mm3;
24. Total white blood cell count <3,000/mm3;
25. Pregnant or lactating female; positive pregnancy test, women of childbearing potential must be tested;
26. Non-ambulatory patients;
27. Patient with a history of right heart failure occurring as a consequence of, for example, biventricular failure, intrinsic pulmonary disease, chronic thromboembolic pulmonary hypertension, and other etiologies that result in elevated right-sided pressures.

5.4 Informed Consent

Written, study-specific Informed Consent will be obtained from each subject prior to treatment with the BlueLeaf System. The Investigator will keep the original ICF and a copy will be given to the subject. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for a total of five years.

5.5 Primary Safety Endpoint

The primary safety endpoint is the:

- Freedom from deep venous thrombosis (DVT) in the target vessel defined as:
  - Thrombotic occlusion, or
  - Stenosis due to thrombus accounting for > 50% diameter reduction through the 30-day follow-up;

  and/or
- Freedom from symptomatic pulmonary embolism confirmed by contrast-enhanced pulmonary angiography through the 30-day follow-up.

NOTE: 'Target vessel' is defined as the common femoral, proximal femoral, distal femoral and popliteal vein segments, in continuity (including duplications), of the treatment limb.

5.6 Primary Effectiveness Endpoint

The primary acute procedural success endpoint is evidence of hemodynamic effect as demonstrated by Intravascular ultrasound (IVUS) and/or venographic based evidence of pocket filling accompanied by leaflet or pocket mobility, at any autogenous valve sites.

5.7 Secondary Endpoints

The following will be secondary endpoint measures:

- Freedom from target vessel deep venous thrombosis (DVT) in the primary treated vein segment at 90, 210, and 360 day follow-up imaging study.
- Additional Outcome Measures

  The following will be additional outcome measures:
  - All-cause mortality;
  - PE as defined above beyond 30-day follow-up;
  - Major bleeding, defined as Type 3a or greater bleeding using the Bleeding Academic Research Consortium criteria;
  - Mural thickening or thrombus deposition not qualifying as a target vessel DVT;
  - For CEAP 6 subjects, progression/regression of venous ulcer area, as expressed by total area of ulceration in the target limb;

- Post-procedural Reflux Time (RT) of each individual autogenous valve and volumetric flow rates within a target vessel by DUS as detailed in the Imaging Manual of Operations;
- APG indices for subjects evaluated with APG as measured with change from baseline, including Venous Volume (VV), Ejection Fraction (EF) and Residual Volume Fraction (RVF) and Venous Filling Index (VFI);
- Disease-specific Quality of life indices, including rVCSS and VEINES-QOL/Sym;
- General patient reported outcome survey such as the SF-36;
- Technical success, defined as delivery of the system to the target vessel and formation of at least one mobile autogenous valve (as measured with IVUS following valve formation) without target vessel occlusion at the conclusion of the index procedure.
- CVI symptom evaluation, including Visual Analog (VAS) pain score and calf swelling

5.8 Study Assessments

The following study procedures and assessments will be required as noted in Table 1. A more complete description of the imaging assessments are included in the Imaging Manual of Operations. In case of any discrepancies between this protocol and the Imaging Manual of Operations, the Imaging Manual of Operations will be followed.

Compression Therapy Use:

Baseline and study duration compression therapy use information will be collected for all subjects at each follow up visit. The type (i.e. 20-30 mm HG below-knee compression hose) and frequency of use (i.e. daily use) should be documented.

Recommended post-procedural compression use is described in section 6.7.

Wound Care Regimen:

Baseline and study duration wound care regimen information (frequency of visits to a wound clinic and note of type of treatments received) will be collected for subjects presenting with leg wounds upon enrollment. Wound care regimen information will continue to be collected for these subjects for the duration of their study follow up. If a leg wound develops during the study for any subject, this same wound care regimen information will be collected upon first presentation of the wound and for the duration study participation.

Recommended post-procedural wound care is described in section 6.7.

Photography:

Subjects with leg ulcers upon enrollment must have photography of the ulcers at each visit where at least one ulcer is present. If an ulcer is completely healed during the course of follow-up, photography will be completed at the first visit following ulcer healing, but not in subsequent visits, unless an ulcer

recurrence occurs. Ulcer healing will also be documented in the source documents and on the follow-up case report form (CRF).

When photography is conducted, at least two photos of each ulcer will be obtained with a ruler present in the field of view of each photo. If more than one ulcer is present, additional photos of the subject's entire leg will be obtained to orient the reviewer to the individual ulcer photos. Specific photography-based ulcer tracking technologies may be used as long as the photography requirements described are met. A copy of each photo will be submitted to the Sponsor and each will be labeled by location. No photo will include the subject's face or other personal identifiers in the frame.

The Imaging Manual of Operations should be referred to for additional details.

Duplex Ultrasound:

In the screening phase, color-flow duplex ultrasound will be obtained to document target vessel patency, reflux and other relevant subject screening information, with subject in the supine and standing positions, per specific guidelines outlined in the Imaging Manual of Operations. Waveform analysis of the common femoral vein will be used to rule out subjects with obvious outflow obstructions. Baseline RT and volumetric measurements will be made in the femoral, and popliteal veins, with the subject in the standing position.

In study follow-up visits, views of each formed autogenous valve will be obtained and quantitative and qualitative data will be taken. Qualitative assessments, such as leaflet mobility, and flow reversal will be taken for each treatment site. Baseline RT and volumetric measurements will be made in the femoral, and popliteal veins, with the subject in the standing position.

Specific parameters for duplex procedures, such as use of an automated calf cuff, manual augmentation, and subject positioning will be provided in the Imaging Manual of Operations, and must be adhered to, in order to insure consistency between subjects and between visits.

Volumetric measurements involve utilizing a volumetric measurement program that is included within all modern DUS machines to capture a time averaged value of reflux velocity, in addition to the duration of reflux captured in the RT measurement. Furthermore, the sonographer is instructed to measure the luminal diameter of the vessel at the measurement location, so that a volumetric reflux value can be calculated. Volumetric measurements are taken concurrently with the RT measurements, and require no additional equipment.

Venography:

Contrast venography will be performed prior to commencement of the index procedure. The access site may be chosen at the Investigator's discretion. Access will be achieved percutaneously using ultrasound guidance or through an open surgical venous exposure. The venogram will be performed with a scale present in the field of view.

The screening venogram should include views of the ipsilateral outflow vessels, including the femoral, common femoral, external iliac and common iliac veins to assess outflow obstruction, although

definitive exclusion for outflow obstruction is determined with intravascular ultrasound. The contrast will be injected into the femoral or more caudal vein to assess outflow from the femoral vein (common femoral vein, external iliac vein, and central iliac vein). Pre-procedurally, a controlled bolus contrast venography should be performed as specified in the Imaging Manual of Operations. Additionally, the extent of flow limiting post-thrombotic venous change in the femoropopliteal segment will be assessed.

The status of femoropopliteal reflux must be subjectively classified by the Investigator as either present or absent to aid in assessment of deep vein reflux. Presence of any competent vein valves between the access site and the most proximal potential treatment site must be identified for subject exclusion. The pre-intervention diagnostic venogram will be recorded digitally using Digital Imaging and Communications in Medicine (DICOM) format and submitted to the core laboratory.

Contrast venography will be performed following completion of each autogenous vein valve formed, assessing the amount of residual reflux and the extent of any vessel damage visualized, and the degree of vessel stenosis at the site of the target sites. The post-intervention venograms will be recorded digitally and submitted to the core laboratory. The last contrast venography performed, after the highest autogenous valve formed, should be initiated from the same location as the baseline contrast venography performed before the procedure, with the same controlled bolus, as specified in the Imaging Manual of Operations.

IVUS:

IVUS will be performed using machines and probes at the Investigation's discretion, but with appropriate MHz frequency to adequately visualize the target sites. An initial, diagnostic IVUS will be performed to assess the presence and extent of any outflow obstruction central to the planned level of autogenous valve construction, to include the ipsilateral femoral vein, and the common femoral, external iliac and common iliac veins. The diameter, perimeters, and cross-sectional area and location of the target sites will be measured with IVUS, as will the presence of any webs, spurs or synechiae in the target vessel or ipsilateral central outflow vessels. These parameters will be entered into the procedure CRF and IVUS images will be recorded digitally and submitted to the core laboratory. Reference diameters, perimeters, and cross-sectional areas of the proximal femoral, distal femoral and popliteal veins will also be taken prior to any treatment.

During the valve creation procedure, after the formation of each new autogenous leaflet, IVUS will be utilized to assess certain parameters such as leaflet length, leaflet width at body, leaflet width at opening, and leaflet thickness, as shown in Figure 5. Leaflet mobility and coaptation will be subjectively graded by the Investigator with IVUS. Coaptation will be objectively assessed by the core laboratory from cine venography images. As well, the core laboratory will use IVUS images to assess the thickness of the newly formed autogenous leaflets and to assess the degree, if any, of venous wall injury at and central to the valves.

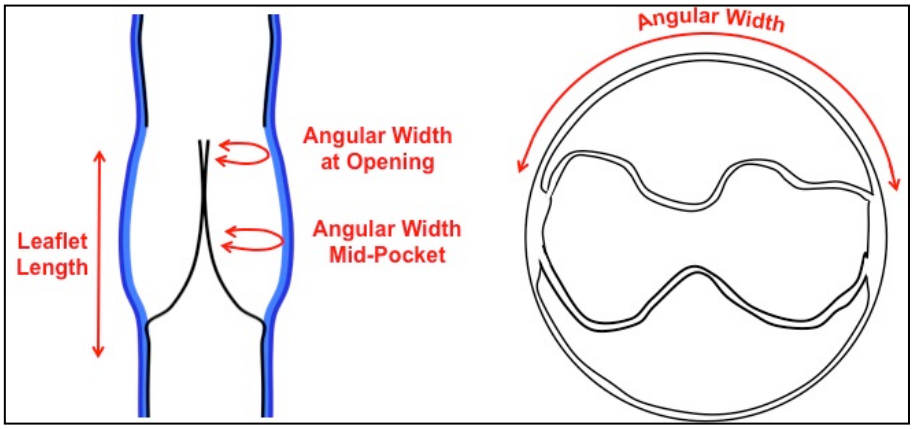


Figure 5. Leaflet dimension guide. Left: side view of critical dimensions for bicuspid valve. Right, top view of critical dimensions for bicuspid valve. Similar values are collected for monocuspid valves as well.

Air plethysmography:

APG is an optional test that a site may choose to perform. Sites performing APG will record the APG tracing and submit them to the Core Laboratory. VV, EF and RVF and VFI will be assessed by the Core Laboratory[10, 23, 29-34]. The method for performing APG can be seen in Figure 6 below and is detailed in the Imaging Manual of Operations. A normal VFI is < 2 mL/s, while VFI values in the 4 - 7 mL/s range or higher tend to correlate with an increased severity of CVI.[35-38] APG appears to be a reliable predictor of venous reflux, providing an estimate of CVI severity and an objective measure of deep reflux and/or perforator reflux.[34] When APG is performed at the baseline, the assessment must be conducted at 7-day, 30-day, 12-week, 210 and 365-day follow-up visits and will be considered per protocol.

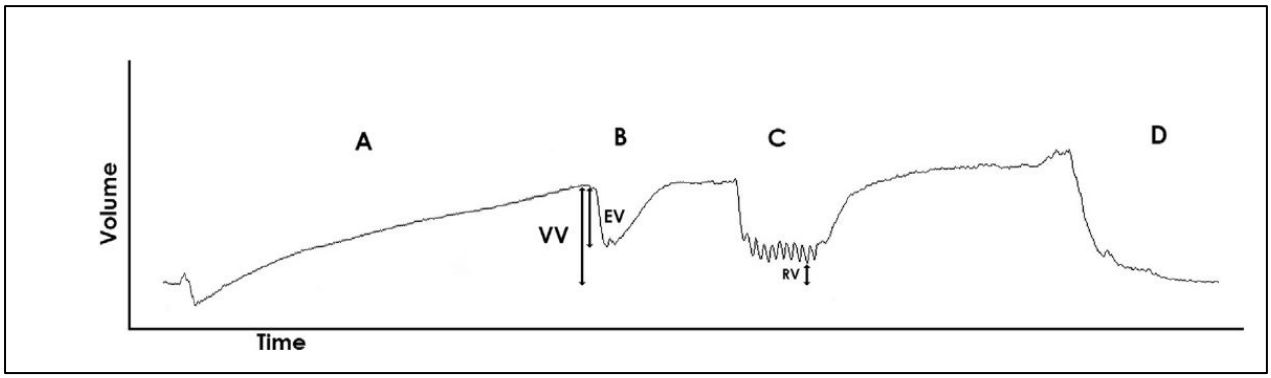


Figure 6. Air plethysmography (APG) curve for testing of reflux and calf muscle function. A. After elevation of the leg, the patient will stand with the weight on the contralateral limb until maximum venous volume (VV) is reached. B. One tiptoe movement. C. Ten tiptoe movements. D. The patient returns to the supine position with the leg elevated. VFI is calculated by dividing 90% of the venous volume by the time needed to fill 90% of the venous volume after returning to an upright position. Ejection fraction (EF) equals ejection volume (EV)/VV x 100%. Residual volume fraction (RVF) equals residual volume (RV)/VV x 100%. Reproduced from Kurstjens, et al32

Revised Venous Clinical Severity Score:

The rVCSS will be determined for each subject by assigning a severity level (0, 1, 2 or 3) to each of the ten attributes of venous disease. The rVCSS is provided in Appendix A.

The rVCSS evaluation and CEAP classification must be completed within 14 days of the index procedure.

Pain VAS Score:

A pain VAS (visual analogue scale) is a unidimensional measure of pain intensity. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the subject's mark, providing a range of scores from 0–100, where a higher score indicates greater pain intensity.

Patient Reported Outcome Survey:

(such as the Short Form, SF-36) The short form survey, SF-36, or similar, will be completed to capture general patient reported health outcomes. The SF-36 is provided in Appendix A.

VEINES-QOL/Sym Questionnaire:

The VEINES-QOL/Sym is a patient-based questionnaire that is designed for self-completion. The questionnaire measures the impact of CVI-related symptoms and quality of life from the patient's perspective. Questions cover symptoms, limitations in daily activities, time of day of greatest intensity, changes over time, and psychological impact. The questionnaire is provided in Appendix A.

Table 1. Schedule of Study Procedures and Assessments

Evaluation	Screening		Pre-discharge	7-day Visit	30-day Visit	90-day Visit	210[e]-day Visit	360-day Visit
	Pre-Procedure	Procedure						
Assessment Window	- 2 m	NA	NA	± 3d	± 14d	± 21d	± 30d	± 60d
Medical History	X							
Blood Tests	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Pregnancy Test[b]	X							
Physical Examination	X			X	X	X	X	X
Compression Therapy Usage	X			X	X	X	X	X
Wound Care Regimen	X			X	X	X	X	X
Photograph of ulcer[c]	X	X[f]		X	X	X	X	X
Duplex Ultrasound	X		X[a]	X	X	X	X	X
Venography	X[d]	X						
Intravascular Ultrasound	X[d]	X						
Air plethysmography (optional)	X			X	X			X
rVCSS[27]	X	X			X	X	X	X
SF-36	X				X	X	X	X
VEINES-QOL/Sym[28]	X				X	X	X	X
Pain VAS Score	X				X	X	X	X
Adverse Event Reporting	X	X	X	X	X	X	X	X

[a] If the discharge date falls within the 7-day visit schedule window (4-10 days post-procedure), a pre-discharge DUS is not required, only the one for 7day.

[b] Pregnancy test required only in females of reproductive potential.

[c] Required only in CEAP 6 subjects at time of enrollment.

[d] An additional venography or IVUS may be performed prior to the day of the index procedure to assess outflow obstruction.

[e] The 210-day visit is scheduled to collect data at least 4 weeks after discontinuation of anticoagulant therapy in subjects not requiring anticoagulation therapy for more than 168 days.

[f] Peri-procedural ulcer photography may be performed any time during the index procedure visit, preferably before the index procedure.

Subsequent annual visits (through a total of 5 years) will follow the 90-day schedule of assessments with a visit window of ±60d.

6 INVESTIGATIONAL PROCEDURE AND POST-PROCEDURAL CARE

6.1 Preparation of the Subject for the Procedure

The subject will be prepared for the planned index procedure according to standard hospital procedures. The planned access site, either the ipsilateral common femoral or femoral vein, will be prepared and draped in a sterile manner. Local, regional or general anesthesia will be used at the operator's discretion. Venous access may be obtained with an open surgical exposure or percutaneously. Venous access must be performed under ultrasound guidance if done percutaneously.

6.2 Periprocedural Medications

The anticoagulation/antithrombotic regimen is specified in Table 2.

Subjects will be treated with antiplatelet agents beginning on the day of the procedure and continued for at least 90 days thereafter. Aspirin is required, and use of Clopidogrel or Prasugrel is optional per investigator preference.

Once venous access has been safely obtained, the subject will be anticoagulated with unfractionated heparin to achieve an Activated Clotting Time (ACT) of at least 250 seconds or a level corresponding to the local standard of care. Heparinization should be continued with repeated boluses or a continuous intravenous infusion, at the operator's discretion, to maintain an adequate ACT throughout the interventional procedure. Unfractionated heparin anticoagulation will be discontinued at the conclusion of the procedure unless investigator(s) choose to maintain lower doses of unfractionated heparin up until discharge. The use of protamine sulfate is discouraged.

Post-procedurally, investigators have two options for anticoagulation:

Option 1:

Enoxaparin (e.g. Lovinox or Clexane) is begun within 2 hours of index procedure, using a weight-based twice daily administration (1mg/kg q 12h). Subjects may be assisted with training and administration of Enoxaparin injections by healthcare personnel engaged by the study Sponsor. Enoxaparin is continued for at least 7 days at this dosage, and is not discontinued until INR ≥2.5. Warfarin is begun day of index procedure or the day after, and is administered per local Standard of Care (SOC) for therapeutic dosage. Warfarin is continued for at least 168 days post-index procedure unless bleeding complications occur.

Option 2:

Enoxaparin (e.g. Lovinox or Clexane) is begun within 2 hours of index procedure, using a weight-based twice daily administration (1mg/kg q 12h). Subjects may be assisted with training and administration of Enoxaparin injections by healthcare personnel engaged by the study sponsor. Enoxaparin is continued for at least 7 days at this dosage. Direct Oral Anticoagulant (DOAC) such as Rivaroxaban, Dabigatran, or Apixaban is begun no more than 12 hours following discontinuation of enoxaparin at a therapeutic dose as typical for acute DVT per local SOC, and is continued for at least 168 days post-index procedure unless bleeding complications occur.

As the initial 7 day twice daily administration of Enoxaparin is considered a key safety requirement, the time and date of each injection will be captured and recorded on paper daily for each subject through the 7 day post-procedure period. It must be entered into the electronic data capture (EDC) system by at least the day 7 visit. If the 7-day visit occurs before 7 days have elapsed since the procedure, those times and dates of each injection up through 7 days that were not accounted for at the 7-day visit, will be input at the next visit. Longer use of Enoxaparin will be tracked with other concomitant medications without the daily time of administration required to be recorded.

Table 2. Anticoagulation and antithrombotic regimens

Agent		Start	Stop	Notes
Antiplatelet (Clopidogrel or Prasugrel are optional as stated above):				
Aspirin		On day of and prior to index procedure	At least 90-days post-index procedure	Recommended dosage: 100mg daily
Procedural Anticoagulation:				
Unfractionated heparin		After access achieved	After intervention (or may be continued at lower doses until discharge)	Bolus at time of procedure to achieve at least an ACT of 250s, and intermittent bolus to maintain ACT
Post-Procedural Anticoagulation: Utilize either Option 1 or Option 2 below:				
Option 1	Enoxaparin	Within 2 hr of index procedure	At least 7 days post-index procedure, but not until INR ≥2.5	Required dosage: 1mg/kg q 12h
	Warfarin	Day of index procedure or day after	At least 168 days post-index procedure unless bleeding complication occurs	Therapeutic dosage per local SOC
Option 2	Enoxaparin	Within 2 hr of index procedure	At least 7 days post-index procedure	Required dosage: 1mg/kg q 12h
	DOAC (Rivaroxaban, Dabigatran or Apixaban)	No more than 12 hours after discontinuation of Enoxaparin	At least 168 days post-index procedure, unless bleeding complication occurs	Therapeutic dosage for acute DVT per local SOC

ACT, Activated clotting time; INR, International normalized ratio; SOC, Standard of care.

6.3 Diagnostic Venogram and IVUS

The diagnostic venogram will be performed per standard of care but must provide adequate visualization of the target vessel.

IVUS will be performed using standard of care, with visualization of the target vessel over the length of target sites where autogenous valves will be formed as well as into the outflow vessels.

The diagnostic venogram and IVUS procedures may be carried out on the same day as the investigational procedure, or if deemed appropriate by study investigators, may be performed anytime within 2 months of the investigational procedure.

6.4 Formation of the Autogenous Valve Leaflets

Access for the investigational procedure will be performed through an ipsilateral common femoral vein or femoral vein approach. The autogenous valves will be constructed as described in the IFU, with the procedural goal being to create a single, competent autogenous valve (monocuspid or bicuspid). A leaflet formation attempt shall be defined as the dissector tool being actuated at least once, after being inserted into the vein wall at a particular angular and longitudinal position.

6.5 Completion Venography and IVUS

Following completion of each autogenous valve leaflet, IVUS will be used to assess leaflet mobility and coaptation. Following completion of each autogenous valve (at a particular vein level), contrast venography will also be performed according to standard of care. IVUS will be used to capture study specific valve information as detailed in Figure 5.

6.6 Sheath/Guide Removal

It is important to refrain from occluding the femoral vein outflow when applying manual pressure after sheath/guide removal. Ultrasound may be used to assure continued flow through the femoral vein at this time, at the discretion of the operator.

6.7 Post-procedural Care Regimen

Following the procedure, and after the investigator has assured access site hemostasis, the subject should ambulate as often as feasible. The subject should wear medium-level (e.g. 15-20 mm Hg) below-knee level compression hose when out of bed. The use of compression hose must continue for at least the first 30 days after the investigational procedure. The compression hose can be removed when in bed, at the subject's discretion. Intermittent pneumatic compression (IPC) devices, if available, should be used for at least the 7 days after the procedure and the subject is encouraged to use the devices whenever they are non-mobile. After the 30-day follow-up visit, the subject should return to his or her pre-procedure compression level both in type and frequency. For example, if the subject is regularly using 10-20 mm HG below-knee compression hose prior to the study procedure, the subject should continue on regular use of 10-20 mm HG compression hose after the 30-day follow-up visit is completed. If the subject is not using any compression hose prior to the study procedure (but is still included in the study due to prior history of failed conservative therapy), the subject should discontinue compression after the 30-day follow-up visit is completed, unless otherwise specified by investigator. The use of compression hose and IPC devices is recommended but not mandatory; thus, the failure to comply will not be considered a protocol deviation but the reason for non-compliance is to be recorded. Compression therapy usage will be tracked at each study follow-up visit.

Strict compliance with the post-procedural anticoagulation/antithrombotic regimens described in Table 2 is required. Extended travel before the 7-day follow-up visit, including but not limited to air travel, is strongly discouraged, and the Sponsor is willing to offer reasonable accommodations local to the investigational site to accommodate non-local subjects between discharge and the 7-day follow-up visit.

Reasonable measures may be undertaken to promote compliance with anticoagulation/antithrombotic regimens, compression therapy, and mobility. A log of enoxaparin injection times and dates for all post-procedural days up to and including the day of the 7-day follow-up visit must be maintained and logged into the appropriate CRF. The log also includes information on subject compliance with compression and mobility. The exact mechanisms for promoting compliance will vary from site to site, but some examples of reasonable measures include but are not limited to:

- at-home (or in-hotel) nursing services;

- third party nursing or research coordinator phone calls, or other communication efforts to track and promote compliance;
- outpatient administration of enoxaparin shots by clinical site staff.

The type and frequency of wound care for subjects with active venous ulcers is not explicitly defined, and should be per local standard of care. It is recommended that the subject receive the same type and frequency of wound care pre- and post-procedure, as long as that falls within the local standard of care. Subjects with active ulcers, not receiving sufficient wound care prior to study enrollment, should be further evaluated for ability to resolve symptoms with conservative measures prior to study enrollment in alignment with inclusion criteria #8.

7 INVESTIGATIONAL DEVICE ACCOUNTABILITY

It is expected that an average of approximately 1.5 BlueLeaf Systems per subject will be used.

7.1 Accountability of Investigational Devices

Each batch of devices will be assigned, at a minimum, a lot number which will be used for tracking purposes. Device inventory will be managed using the Device Accountability Log which will include details concerning device receipt and disposition.

Access to device inventory will be controlled and devices will be housed in a secure location. Records will be maintained to document the physical location of inventory from shipment/removal from Sponsor manufacturing facility through use and/or return or disposal.

The investigational sites will be responsible for keeping records of receipt, use, return and disposal of the investigation device which shall include, at a minimum, date of receipt, device identification number, expiration date, date of use, subject identification code, and date of disposition. The Device Accountability Log is provided for this purpose.

The disposable system components will be disposed of as per standard institutional practice.

If the device is associated with a possible device-related adverse event or device deficiency, the device should be returned to InterVene, Inc. for evaluation.

In the event of product return, InterVene, Inc. must be contacted prior to product return for handling instructions.

7.2 Other Devices and Equipment

In addition to the investigational device, a table mount interface system will be provided by Sponsor (Top Mount Single Arm with QC Fitting And Rail Clamp, Model 73000-TM from Mediflex or similar). The following supplies are also required and are the responsibility of the investigative site. See the IFU for specific recommendations for each item.

- Introducer Sheath

- Intravascular Imaging Catheter and Corresponding Imaging Capital Equipment
- Inflation Device
- 0.035 guidewire (180cm length minimum)
- Syringes, stopcocks, RHV, extension lines and other standard interventional accessories

These items are available commercially for the indications for which they are proposed in this study and will not be tracked with the device accountability system and log.

8 STATISTICS AND DATA ANALYSIS

8.1 Statistical Methodology

This is a descriptive study and, as such no performance goals have been defined for the primary safety or effectiveness endpoints.

8.2 Sample Size Calculation

There is no formal sample size calculation in this descriptive, non-hypothesis generating clinical study.

8.3 Study Visit Window

The follow-up visit windows that will be used for analysis are specified in Table 1.

8.4 Missing Data

Best efforts will be made to minimize the amount of missing data. Imputation of missing data will not be performed.

8.5 Demographics and Baseline Characteristics

The baseline demographics and anatomic characteristics of the treatment group will be presented with descriptive statistics.

8.6 Analysis of the Primary Safety Endpoint

Descriptive statistics (frequency and percentage) will be calculated for the primary safety endpoint.

8.7 Analysis of the Primary Effectiveness Endpoint

Descriptive statistics (frequency and percentage) will be calculated for the primary effectiveness endpoint.

8.8 Analysis of Follow-Up Observations

Descriptive statistics will be calculated for all secondary observations, with frequency and percentage for categorical variables and mean (or median) and standard deviation (or range) for continuous variables.

8.9 Subgroup and Other Analyses

No subgroup analyses are planned for this study.

8.10 Interim Analyses

The DSMB will review safety data (including components of the primary effectiveness endpoint to the extent that safety is impacted) to ensure that it is ethical to continue the study, based on the absence of unacceptable risks to the subject. There will be no formal interim effectiveness analysis of the primary endpoints.

9 ASSESSMENTS AND FOLLOW-UP SCHEDULE

Subjects will undergo the assessments depicted in the Schedule of Assessments (Table 1.)

9.1 Screening/Baseline Assessment

An initial evaluation will be used to determine if a subject may be considered for enrollment. This evaluation includes an assessment of diagnostic testing that would have been done as part of a subject's routine care. If the initial assessment shows that the subject may be potential study candidate, the subject may be approached for study participation and informed of the risks and benefits of the study. If the subject provides written informed consent, then all inclusion/exclusion criteria are to be evaluated. The final disposition (e.g., enrollment, ineligibility, or decision by the subject or physician not to enroll) must be noted.

The data captured for the Screening Visit may be gathered over the course of more than one office visit; however, the data must have been obtained within 2 months of the scheduled procedure date. The following procedures will be performed at the Screening visit prior to the procedure and all data must be recorded in the subject's CRF:

- Demographic information
- Medical history including risk factors
- Physical examination with ankle-brachial index
- Compression therapy utilization (last 3 months)
- Ulcer and wound care history (i.e. onset date of longest current active ulcer and recent utilization of wound care, if applicable)
- Ulcer photography (if applicable)
- Screening laboratory values to include hemoglobin, platelet count, total white blood cell count, and serum creatinine.
    - Clinical laboratory tests are expected to be performed at this visit to establish baseline levels. It is recognized that specific panels may vary between institutions. Laboratory data will not be specially analyzed but will be used only to support adverse event evaluations.
- Duplex ultrasound

  IMPORTANT: The DUS imaging must be submitted to independent medical reviewer to confirm anatomical eligibility prior to performing the procedure.

    - The quality of the DUS must also be confirmed by the duplex imaging core lab prior to performing the procedure.
- APG testing, if performed
- Quality of life indices, general and disease-specific
- Serum or urine pregnancy test for females of childbearing potential.
    - The test must be negative at baseline and subject must be using a medically acceptable method of birth control. Acceptable methods of birth control include: barrier method with spermicide, steroidal contraceptive, contraceptives in conjunction with a barrier method, intrauterine device, or abstinence. No pregnancy test is required for post-menopausal women or women who are surgically sterile.

The procedure will be scheduled to allow InterVene personnel attendance.

9.2 Point of Enrollment

A subject is considered enrolled in the study after he/she has provided written informed consent.

9.3 Treatment Assessment

The procedure is conducted under fluoroscopic/venographic and IVUS guidance. Refer to the IFU for techniques and methods for device use.

Anticoagulation therapy to ensure an ACT of at least 250 seconds is recommended. Investigator discretion is advised regarding antiplatelet therapy and blood pressure adjustment.

Subjects who require conversion to open surgery due to treatment failure with the device will be followed at each of the follow-up visits specified in Table 1.

The following data are to be recorded on the subject's Procedure CRF.

- Venous access site
- Number and location of created valves, including attempted but unsuccessful
- Blood loss and replacement fluids (blood products) administered
- Required unplanned additional/adjunctive procedures
- Adverse events and device deficiencies that occur during the index procedure
- Procedure time (access stick to last sheath/guide removed)
- Device time (introduction of study device to removal of study device)

9.4 Follow-Up Assessments

Each follow-up assessment will include a duplex ultrasound study to evaluate target vessel patency and valvular function. An APG may also be obtained as specified in Table 1. Imaging studies and the APG do not need to be performed on the same day as the scheduled follow-up visit.

9.5 Unscheduled Follow-up Visits

If a subject returns to the investigator for clinical follow-up visits or undergoes imaging studies not protocol-specified but for matters related to the study procedure, such visits will be considered unscheduled visits. The assessments completed at such visits will be performed at the discretion of the Investigator. CRF pages are provided for unscheduled visits and contain the same information as all the follow-up visits, in addition to the reason for the visit.

9.6 Study Exit, Withdrawal and Lost to Follow-Up

Participation is completely voluntary and each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw the subject from the study in the event of illness, adverse events or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw for any reason, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal must be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

Subjects will be exited from the study by completing a Study Exit CRF at the time of study completion provided the subject has not experienced an adverse event that is ongoing and unexplained, or, in the opinion of the Investigator, requires continued monitoring. Following study exit, the subject will undergo standard medical care for their condition as determined necessary and appropriate by their physician.

Subjects may be prematurely terminated or withdrawn from the study for the following reasons:

- Death
- Voluntary withdrawal whereby the subject voluntarily chooses not to further participate in the study. In this case, the data collected up to the time of withdrawal will remain in the analytic dataset.
- Lost to follow-up. The subject is more than one month late to a study visit and three documented attempts to contact the subject are unsuccessful. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up. A missed visit will be considered a protocol deviation and the deviation will be documented and reported.
- In the Investigator's opinion, it is not in the best interest of the subject to continue study participation.

Successful autogenous valve formation is defined as any % decrease in RT for any treated vein segment as compared to the corresponding baseline measurement for that vein segment, at the first post-procedural imaging study. If it is determined that autogenous valves were never successfully formed; or if, at any point after the procedure, it is determined that:

- all autogenous valves are confirmed to have re-adhered to the vein wall, or
- no autogenous valves can be visualized in a duplex follow-up exam and, in the same exam, no autogenous valves continue to provide improvement in venous function (defined as having a %

decrease in RT for any treated vein segment as compared to the corresponding baseline measurement for that vein segment), or
- the target vessel has had a DVT,

subjects must be followed for at least 90 days post index procedure for safety and then may be exited from the study at the discretion of the Investigator or Subject. If any of these items are discovered after 90 days post index procedure, the subject may be exited from the study at that time, provided there are no ongoing AEs or ongoing clinical questions related to the procedure that, in the opinion of the investigator, require continued monitoring. Note that it is preferable to have the Subject remain in the study and complete any remaining follow-up visits per protocol.

All subjects treated with the study device, including those withdrawn or lost to follow-up, shall be accounted for and documented. The reason for and date of withdrawal must be recorded on the subject's End of Study CRF. If the reason for the withdrawal is a device-related or procedure related adverse event (AE), the event must be reported to the Sponsor and recorded in the CRF. If a subject is exited from the study before the last day of any window, any required visits or imaging studies within that window that were not performed will not be considered missed for the purposes of protocol compliance.

10 STUDY MANAGEMENT CONSIDERATIONS

10.1 Data Management: Collection of Clinical Data

The Sponsor and/or assigned designee will be responsible for the processing and quality control of the data. Source data will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later at detailed in section 13.4.2.

10.2 Publication

The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement.

10.3 Protocol Modifications

No changes from the final approved (signed) protocol will be initiated without appropriate regulatory oversight including the regulatory body (including EC) review and approval as appropriate except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator will acknowledge the amendment by signing the Protocol Agreement.

10.4 Protocol Deviations

A protocol deviation is the non-adherence to or divergence from the protocol-specific study procedures or assessments. For example, divergence from the specified inclusion and exclusion criteria, deviations from the schedule of required follow-up assessments, improper or lack of consent, and lack of EC approval, would all be considered protocol deviations. A protocol deviation undertaken to protect the life or physical well-being of the subject in an emergency is a special circumstance that must be reported to the Sponsor and the reviewing EC within 5 working days. No other type of prospective protocol

deviation is permitted without prior approval. A record of all protocol deviations will be maintained and reviewed throughout the conduct of the study. The Sponsor will address deviations and take appropriate corresponding action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

10.5 Information to Study Personnel

The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the study procedures and during the course of the study (e.g., when new staff become involved). The Investigator must ensure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities.

11 DEVICE DEFICIENCIES

11.1 Defining Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

11.2 Reporting of Device Deficiency

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the Sponsor.

12 SAFETY ASSESSMENTS AND ADVERSE EVENT REPORTING

12.1 Clinical Observations

A Clinical observation is defined as an event typically occurring in conjunction with study required procedures or medications which require no treatment or action or minor treatment or action by the patient or healthcare provider. This type of event will not be reported as an adverse event, but rather tracked as a "clinical observation" on a designated CRF. Examples of a clinical observation may be bruising at the groin access site or nausea from the general anesthesia.

If the clinical observation worsens and requires an atypical action or treatment (e.g. intervention is required when it is typically not warranted), the event's status will be elevated from an observation to an adverse event and reported accordingly on an Adverse Event CRF. The Clinical Observation and Adverse Event forms will have unique identifiers assigned that will allow the event to be identified as related.

12.2 Defining Adverse Events

An adverse event is an untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related

to the investigational medical device. This includes an exacerbation of an existing medical condition subsequent to enrollment in a clinical study.

Adverse events are rated in several ways:

- Severity (mild, moderate, severe)
- Anticipated (anticipated, not anticipated)
- Device and procedure relationships (not related, unlikely, possible, probable, causal relationship or relationship unknown).

Adverse events will be categorized as either serious or non-serious. A Serious Adverse Event (SAE) is an adverse event that meets at least one of the following:

- Led to death,
- Led to serious deterioration in the health of the subject, that either:
  - resulted in a life-threatening illness or injury, or
  - resulted in a permanent impairment of a body structure or a body function, or
  - required in-patient hospitalization or prolonged hospitalization, or
  - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

In addition, SAEs for hospitalization or surgery to treat pre-existing conditions, without a serious deterioration in health, will also not be reported as SAEs.

An **adverse device effect** is an adverse event related to the use of an investigational device.

A **serious adverse device effect (SADE)** is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

An **anticipated serious adverse device effect (ASADE)** is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

An **unanticipated serious adverse device effect (USADE)** is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

12.3 Reporting of Adverse Events

Adverse event reporting will start at the initiation of the study procedure (i.e. active preparation of the subject, such as initiating hospital's anesthesia protocol). Adverse events and concomitant medication that occur between the signing of the informed consent and the initiation of the study procedure thus will not be reported on the AE CRFs.

All reportable adverse events must be captured on the Adverse Event CRF. The report should include, wherever possible, severity, duration, outcome, and the Investigator's written medical judgment as to the relationship of the adverse event to the study device, procedure, or underlying disease.

All SAEs and USADEs must be reported to the Sponsor or designee immediately, but no later than3 calendar days of the Investigator's knowledge of the event. The event is reported in the electronic data capture system. The Sponsor will ensure compliance with all country-specific reporting requirements to the appropriate Ethical Committees and Competent Authorities.

Non-serious reportable adverse events are to be submitted via the electronic data capture system in a timely fashion. Certain reportable events may require adjudication; therefore, supporting documentation may be requested to be sent to the Sponsor or designee.

12.4 Classification and Reconciliation of Adverse Events

All adverse events will be reviewed by the study's independent Medical Monitor. Certain categories of adverse events and all USADEs will be reviewed by the Medical Monitor. Where the classification of an adverse event related to seriousness, relatedness, or whether it meets the criteria for an SAE or USADE differs between the Investigator and the Medical Monitor, the classification by the Medical Monitor will be reconciled s the final classification for the analytic dataset. If an investigator or the Medical Monitor cannot assign a causality category to an event's relatedness, the event will be considered possibly related for reporting and analysis.

For events not meeting the criteria for adjudication by the Medical Monitor but where the Investigator and the Medical Monitor differ in one or more elements of event classification, the Medical Monitor's classification will be reconciled as the final classification for the analytic dataset.

13 DEVICE ACCOUNTABILITY

13.1 Accountability and Procedures

a) Each device shipment must be documented on the Device Accountability Log and include the receipt, dispensing, and return of investigational devices.

b) When a shipment is received, the Investigator (or designee) must record on the Device Accountability Log the date received and the Catalog and Lot Number of each device. It is recommended that the Packing List also be signed and dated.

c) Investigational devices must be kept in a secure, limited access storage area under recommended storage conditions (room temperature).

d) During the course of the study, the following information must also be noted on the Device Accountability Log:

e) Identification number of the subject for whom the device was intended

f) Procedure date

g) The Device Accountability Log must be readily available for inspection by representatives from the Sponsor, the EC, and/or other relevant regulatory authorities at any time.

h) The Device Accountability Log and device storage locations will be reviewed during monitoring visits.

i) All unused investigational devices must be returned to the Sponsor once it is determined they will not be used. Upon completion of the study, all unused investigational devices must be returned to the Sponsor if any remain at the site. The monitor is to verify return.

14 STUDY ADMINISTRATION

14.1 Site Initiation

A Site Initiation Visit (SIV) will be conducted by the Sponsor or other appropriate designee (e.g., a CRO) to ensure that all study supplies are present, to ensure proper training of the Investigator and study staff members in study-specific procedures, to ensure regulatory requirements are fulfilled prior to enrollment of the first study subject at a site, and to verify the site facilities and equipment are appropriate for conduct of the study.

The following items will be reviewed at the SIV. All training will be documented and must contain signatures of participants (refer to SIV Training Log in the Regulatory Binder).

a) Introduction and overview of agenda

b) Obligations of the Investigator, including his/her responsibilities to ensure only appropriately qualified staff participate in the study conduct, and notification to the Sponsor or its CRO of any change in staff listed on the Delegation of Authority (refer to the site's Regulatory Binder) during the course of the study

c) Protocol (overall review including, but not limited to, inclusion/exclusion criteria, recruitment/withdrawal of subjects, study restrictions);

d) Completion and maintenance of the Delegation of Authority

e) Adverse experience reporting and USADE reporting

f) CRFs (procedures, corrections, timely completion, retention)

g) Source document preparation and retention

h) Role of the EC

i) Informed Consent Process

j) Study file documents and document retention (ensure all pertinent regulatory documents are collected prior to the site starting the study)

k) Clinical supplies and device management (storage and accountability; device dispensing, labeling, and packaging)

l) Device training

m) Core laboratory processes

n) Requirements for reporting any clinical data back to the Sponsor. (e.g., annual and final reports)

o) Monitoring schedule/plan

p) Other items that may be discussed: background and purpose of the study, previous studies/data, regulatory requirements, policy for publishing trial results, special equipment (if necessary).

14.2 Study Monitoring

Interim monitoring visits will be conducted by InterVene, Inc. personnel or other appropriate designees (e.g., a CRO) to ensure compliance with standard operating procedures (SOPs), the protocol, and other written instructions and regulatory requirements.

The study monitor is the primary liaison between the Sponsor and the Investigator. The main responsibilities of the monitor are to visit the Investigator before, during, and after the study to ensure adherence to the protocol; to verify all data are correctly and completely recorded and reported; and confirm that informed consent is obtained and recorded for each subject before study participation.

The study monitor will contact and visit the Investigator at regular intervals throughout the study. The monitor will be allowed to check and verify the various records (CRFs and other pertinent source data records) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of the study progress, other Sponsor personnel may accompany the study monitor on visits to the study center. The Investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

14.3 Study Termination

InterVene, Inc. may terminate this study at any time. If the study is terminated prior to completion, all subjects currently enrolled will be followed through the study visits as detailed in this protocol. Regulatory authorities have the right to terminate the entire study or a particular study site at any time. Situations that could warrant study termination include, but are not limited to:

a) Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard

b) Insufficient subject enrollment

c) Recurrent protocol non-compliance, violations or deviations

d) Inaccurate, incomplete, and/or untimely data recording (>2 business days) on a recurrent basis

e) Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

14.4 Data Handling and Recordkeeping

Completing, Signing and Archiving Case Report Forms

The Investigator must keep a separate subject identification list showing enrollment numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. It is recommended a note be made in the medical record that the subject is participating in a clinical research study.

The required data will be recorded on the CRFs. Clinical study data will be collected using electronic case report forms (eCRFs). A web-based electronic data capture (EDC) database will be used to record and manage study data. eCRF completion guidelines, the instructions for electronic data-entry, will be developed in conjunction with the Sponsor, the CRO, and/or the EDC vendor.

All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study.

The Investigator will sign the appropriate pages of the eCRF and source documentation. An embedded audit trail will capture the date, time, and user making updates and changes to the electronic data. All data will be entered into the EDC in a timely fashion.

Data Management and Archiving

The Sponsor will be responsible for the processing and quality control of the data. Source data for safety will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later. All other source data, eCRFs, copies of protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, ICFs, and other essential documents must be retained for a period of at least 2 years after the last approval of the marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. Sponsor will inform the Investigator/institution when it is no longer necessary to retain these documents.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

Direct Access to Source Data/Documentation

The Sponsor, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each subject's data. Examples of source documents are hospital records, office visit records, examining

physician's findings or progress notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by Sponsor.

15 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki, this clinical investigation plan, requirements of the approving Ethics Committee, Good Clinical Practices (GCP), ISO 14155 and other applicable regulatory requirements.

This clinical investigation will not be initiated until approval has been obtained from the Ethics Committee and the regulating Competent Authority. Any additional requirements imposed by the Ethics Committee or regulatory authority will be followed. No deviation from the protocol will be implemented without the prior review and approval of the Ethics Committee except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the Ethics Committee as soon as possible.
Clinical trial insurance will be secured prior to initiation of this clinical investigation.

16 ETHICS

16.1 Informed Consent

Written informed consent must be obtained for each subject before any study-specific (non-standard of care) procedures or assessments are done and, specifically, prior to the subject being treated with the BlueLeaf System. Written informed consent will be obtained after the aims, methods, anticipated benefits, and potential hazards are explained.

The subject's willingness to participate in the study will be documented in writing in the study-specific ICF, which will be signed and dated by the subject or Legally Authorized Representative. The Investigator will keep the original ICF and a copy will be given to the subject. It will be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for five years to allow for the ability to collect additional data, in the event that initial study results indicate a need for additional long-term information (i.e., during a post-approval phase).

16.2 Ethics Committee and Regulatory Authority

This study must be approved by an appropriate ethics committee (EC) at each investigational site and any other applicable regulatory authority (e.g. Competent Authority (CA)). Securing EC approval is the responsibility of the Investigator, as defined by ISO 14155-1 prior to starting the study. The Sponsor must receive a copy of the EC approval letter (or equivalent documentation) for the study protocol and ICF before the study can be started at that site or devices shipped to that Investigator.

The EC and Sponsor must approve any significant changes to the protocol as well as a change of Principal Investigator. Documentation of the EC approval must be provided to the Sponsor. Records

of all study review and approval documents must be maintained by the Investigator in the Regulatory Binder and are subject to inspection by the Sponsor or regulatory authority during or after completion of the study. Serious Adverse Events and deaths must also be reported to the EC and Sponsor (reference Section 12 for reporting requirements).

The Investigator must notify the EC, and applicable regulatory authority, as per their reporting guidelines, and the Sponsor when he or she deviates from the protocol. The Sponsor must be notified of all relevant action taken by the EC and must receive a copy of all study-related correspondence between the Investigator and the EC.

At study completion or termination, the EC and applicable regulatory authority must receive notification and a final report is to be submitted in accordance with the applicable regulations. A copy of these reports must be provided to the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the EC.

16.3 Confidentiality Regarding Study Subjects

The Investigator must ensure that best efforts will be made to hold the privacy of all subjects, including their personal identity and all personal medical information. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an individual identification code.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

16.4 Oversight Committees

The DSMB will assure that the study is being conducted ethically. The DSMB membership is represented from the key medical disciplines involved with endovascular repair, and may include an external biostatistician. None of the members is directly involved with the clinical trial.

The Medical Monitor is an individual who is not a direct participant in the study. At the onset of the study, the Medical Monitor will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The Medical Monitor will review and adjudicate appropriate clinical events, mainly related to the device and to the study endpoints.

16.5 Core Reference Laboratories

One or more central core reference laboratories will independently evaluate imaging data collected at participating institutions. All imaging studies that are performed per the protocol must be sent to the Core Laboratory for evaluation. Refer to the Imaging Manual of Operations for details about the identified laboratory and instructions for submitting data.

16.6 Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficient and adequately trained personnel, and availability of potential subjects. No other centers/institutions are intended to participate in this study without permission from the relevant regulatory authority.

16.7 Agreements

All Principal Investigators and their Sub-Investigators must sign an Investigator Agreement. The Sponsor must receive a copy of the signed Investigator Agreement before the study may be started at that institution or devices shipped. Any Investigators joining the study after the site has been initiated may not receive devices or participate until an agreement is signed and received by the Sponsor.

16.8 Responsibilities

Investigator responsibilities include, but are not limited to, the following:

1. Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study subjects

2. Informing all subjects that the device being utilized is for investigational purposes only, and ensuring that the requirements relating to obtaining informed consent and EC approvals are met

3. Ensuring that informed consent is obtained for each study subject in accordance with applicable regulations (e.g., ISO 14155-1)

4. Ensuring that EC approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation

5. Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments

6. Maintaining adequate and accurate records and ensuring those records are available for inspection at any time

7. Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required)

8. Controlling of all investigational devices under investigation.

17 DATA SECURITY AND SCIENTIFIC INTEGRITY

17.1 Access to Data

The Sponsor, auditors, and health authority inspectors (or their agents) will be given access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes, etc.)

for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records (source documentations) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by InterVene, Inc.

17.2 Security and Confidentiality

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (i.e., subject number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may perform source data verification on behalf of the Sponsor or regulatory authorities. Personal medical information will always be treated as confidential.

17.3 Electronic Data

Electronic data will only be accessible to authorized personnel through the use of a unique user ID and password. Passwords are set to expire periodically. Access to electronic study data will be provided to research personnel upon completion of training. Read and write access will be provided to investigational sites but only for information and subject data at their own site. The CRO and the Sponsor will have read-only access and will have the ability to post queries for potential data-related discrepancies.

18 RISK ANALYSIS

18.1 Risks to the Subjects

Treatment with the BlueLeaf System is a procedure that poses significant risks to the subject, although these risks are not expected to be greater than with other endovascular treatment or open surgery. A summary of some of the known risks are identified below however, there may be risks that are not known or are unforeseen at this time. The risks related to the device and to the procedure including those related to concomitant medications used periprocedurally and during follow-up are detailed below. Risks associated with anesthetic methods are not detailed as those methods are site specific and are typically detailed in a separate pre-operative consent.

18.2 General Venous Intervention Risks

Anticipated risks that are associated with general venous interventions, and thus may be encountered in this study but are not considered unique to the BlueLeaf device include but are not limited to:

- Air or thrombotic emboli (venous or arterial)
- Hypotension
- Vascular injury
- Access site complications
    - Bruising
    - Bleeding, hemorrhage
    - Pain
    - Hematoma
    - Infection
    - Wound dehiscence
    - Serous wound drainage
    - Lymphorrhea
    - Ecchymosis
    - False aneurysm due to inadvertent arterial puncture

- Local
    - Leg edema
    - Leg pain
    - Back pain
- Sepsis
- Phlebitis
- Retained foreign body
- Recurrent or worsened venous disease, related to clinical symptoms or pathophysiology
- Radiation exposure related complication
- Reaction to contrast solution
- Complication resulting in death

18.3 BlueLeaf Device and Procedure Risks

Potential risks of the BlueLeaf device and procedure are presented below as event categories, with specific events sub-listed when appropriate. Note that a sub-listed event may fit multiple categories. For example, a “venous perforation” may be a vascular injury during device introduction or positioning or a clinically significant vascular injury due to valve formation steps, depending on which action was being conducted at the time of its occurrence.

- Vascular injury during device introduction or positioning, such as:
    - Venous perforation
    - Arterial perforation
    - Vascular dissection
- Clinically significant vascular injury due to valve formation steps, such as:
    - False venous aneurysm formation

  - False aneurysm formation
  - Vascular occlusion
  - Arteriovenous fistula
- Deep Vein Thrombosis
- Mural Thickening or Mural Thrombus Formation
  - At the autogenous valve site
  - Vascular (not near the autogenous valve site)
- Embolism (thrombus or air), such as:
  - Pulmonary embolism
  - Paradoxical embolization
  - Superficial thrombophlebitis
  - Distal embolization
- Device embolization
- Allergic or adverse reaction to ingredient or agent of concomitant medications used peri-procedurally and during follow-up, contrast or anesthetic
- Allergic or adverse reaction to device materials
- Unusually prolonged clinical procedure, resulting in complications of extended general anesthesia
- Device cannot be removed safely using standard techniques, resulting in unanticipated surgical maneuvers to remove device
- Unsuccessful formation of functional (i.e. hemodynamically active) valves
- Valves are not durable over time and heal in non-functional position

18.4 Concomitant Medication Risks

Potential side effects of the protocol required concomitant medications are reflected in the below lists.

Aspirin

- Black, bloody, or tarry stools
- Coughing up blood
- Severe nausea, vomiting, stomach pain
- Extended fever
- Swelling, or extended pain
- Hearing problems, ringing in ears

Enoxaparin

- Hemorrhage, bleeding
- Anemia
- Thrombocytopenia
- Elevation of serum aminotransferase
- Diarrhea
- Nausea

Warfarin

- Tissue necrosis
- Calciphylaxis
- Systemic atheroemboli and cholesterol microemboli

Direct Oral AntiCoagulant (Apixaban, Dabigatran, Rivaroxaban)

- Uncontrolled bleeding

Further details of risks associated with a specific anesthesia and anticoagulation regimen should be detailed in a separate institution-specific pre-operative consent and/or may be cited from public domain information (e.g. drug manufacturer's labeling). Externally referenced risks for the anesthesia and concomitant medications will be tracked as adverse events but not categorized as unanticipated.

18.5 Risk Mitigation

The Sponsor designed the BlueLeaf System to minimize risks to study participants and the risk management for the system was completed in accordance with ISO 14971.

The clinical investigational protocol, which includes the study eligibility criteria, was also designed to minimize risks to study participants. The eligibility criteria were formulated to limit use of the study device to subjects and venous pathology that fit the device specifications. Subjects will be seen more regularly by study personnel than standard practice for CVI patients which allows more thorough oversight and clinical care. Evaluation of safety data by an independent Medical Monitor and DSMB and assessment of imaging studies by an external core laboratory will provide an ongoing assessment of safety-related events, both individually and in aggregate.

18.6 Benefit to Subjects

It is hoped that the BlueLeaf System will provide an additional treatment alternative for patients with CVI and incompetent deep venous valves. Currently there exist few definitive options for such patients. Conservative measures such as compression stockings and leg elevation treat the symptoms but do not address the underlying venous incompetence Open surgical interventions including venous valve transposition, valvuloplasty, and other surgical methods are invasive and have been associated with suboptimal outcomes. A minimally invasive modality such as endovascular valve construction, if durable, would hold the potential to alleviate the pain, edema, ulceration and other aspects of chronic venous incompetence; an entity that, in its severe form, afflicts up to 10% of the general population.[10, 13, 39, 40]

18.7 Study Justification

This study is justified in light of previous work showing positive outcomes obtained with the use of the study device in peripheral veins. This study will attempt to build on past results and, potentially, identify additional benefits of the BlueLeaf System in patients with symptomatic CVI.

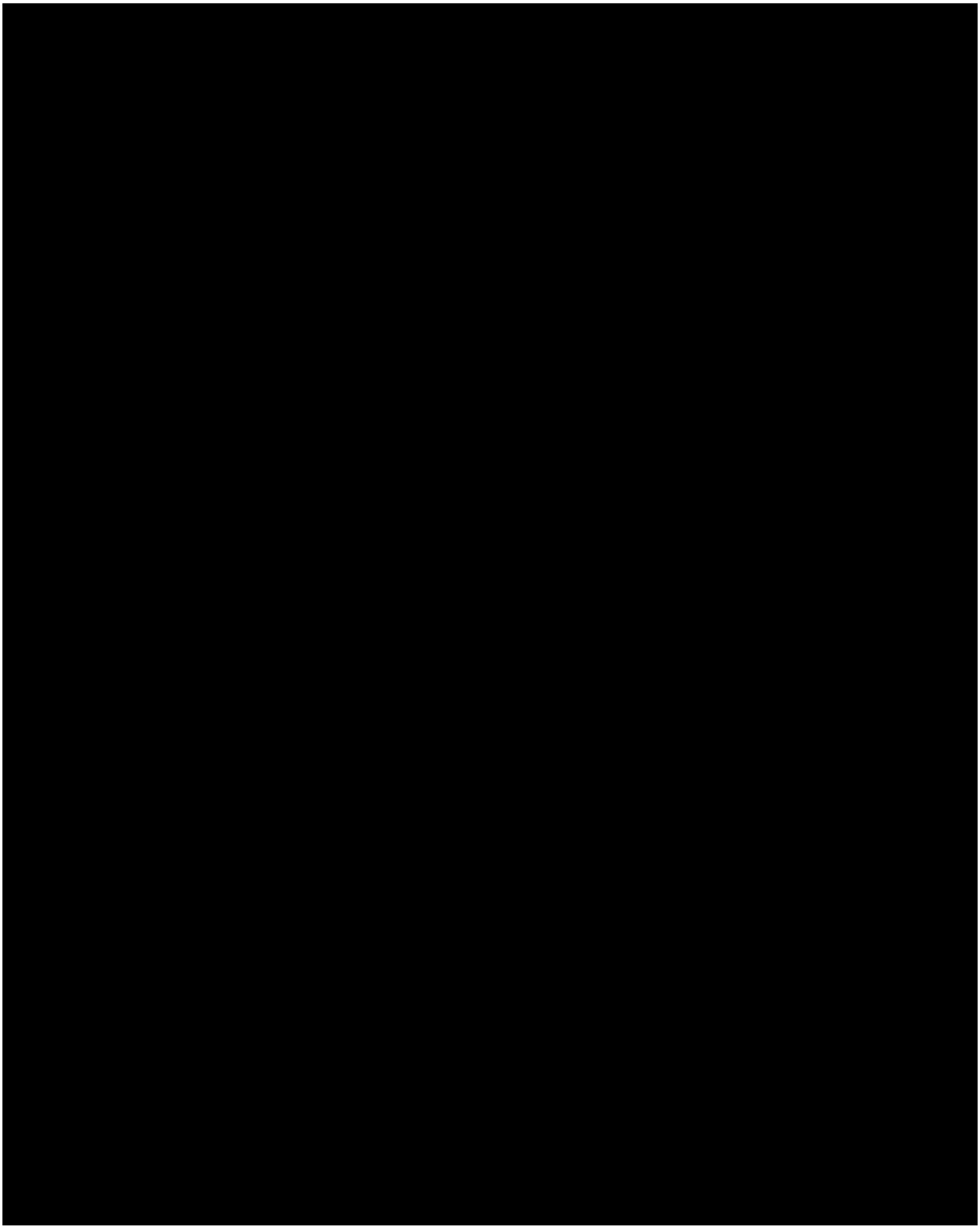
19 ABBREVIATIONS

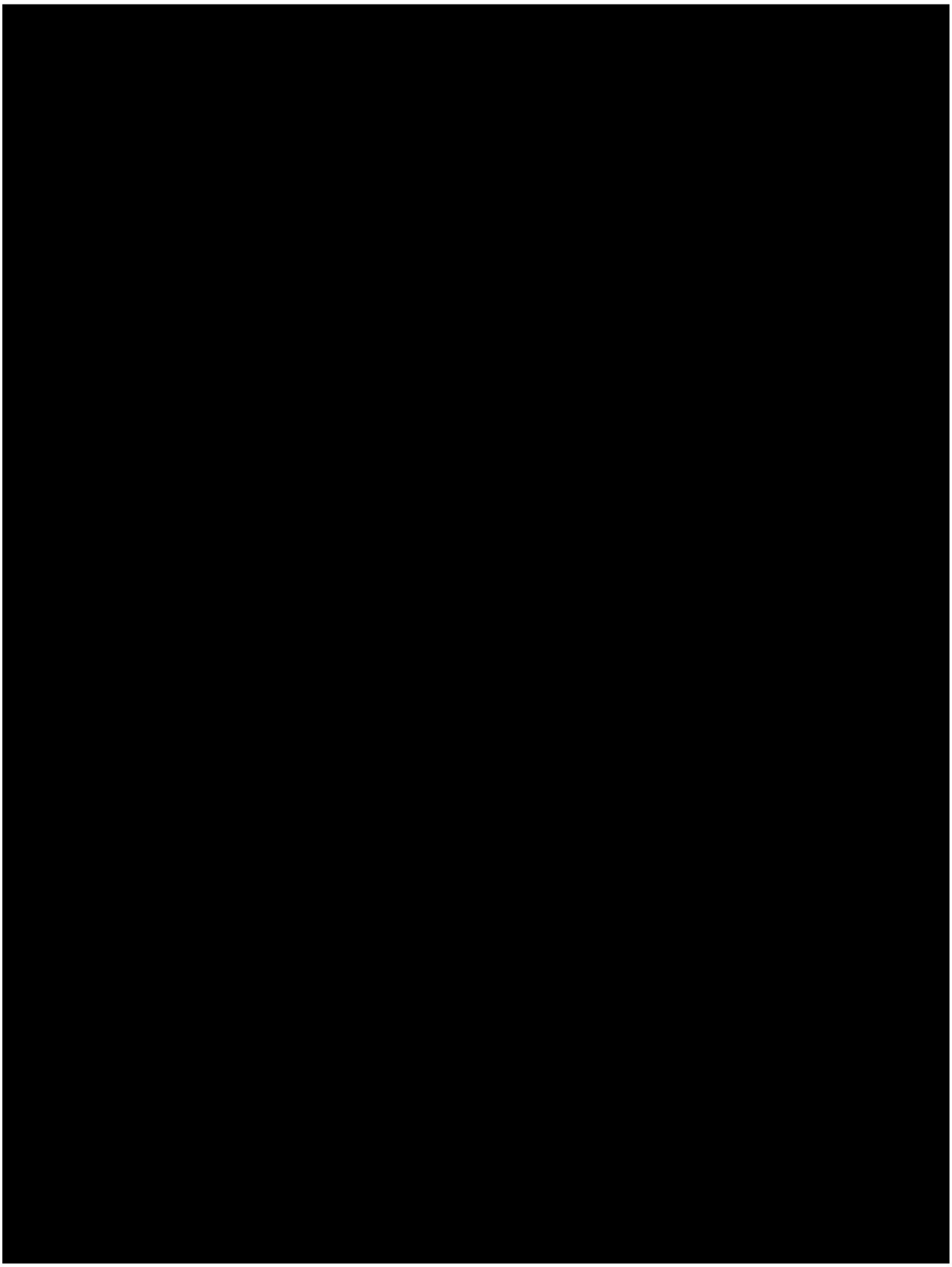
The following abbreviations are used in this document:

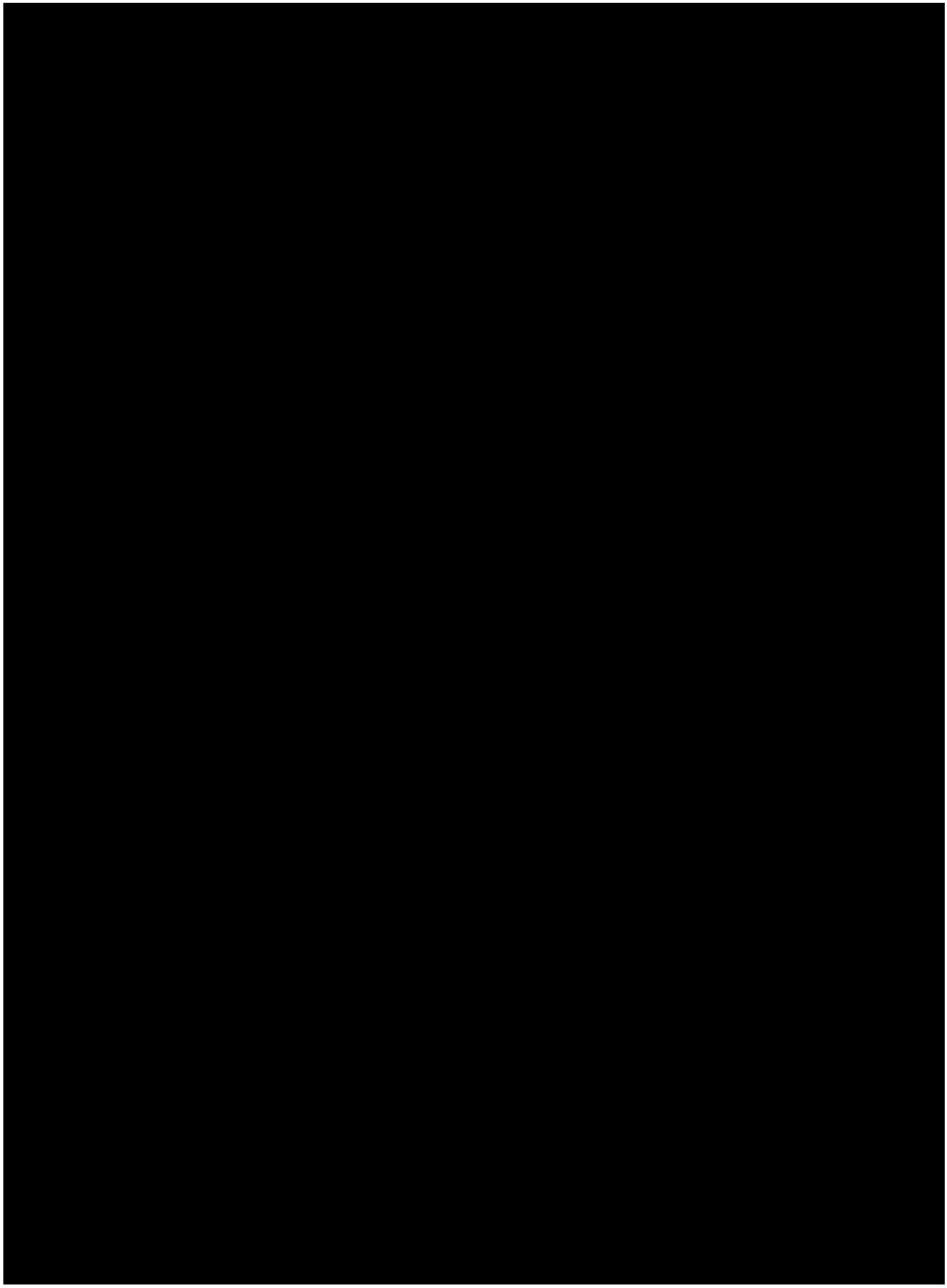
ACT	Activated Clotting Time
AE	Adverse Event
APG	Air Plethysmography

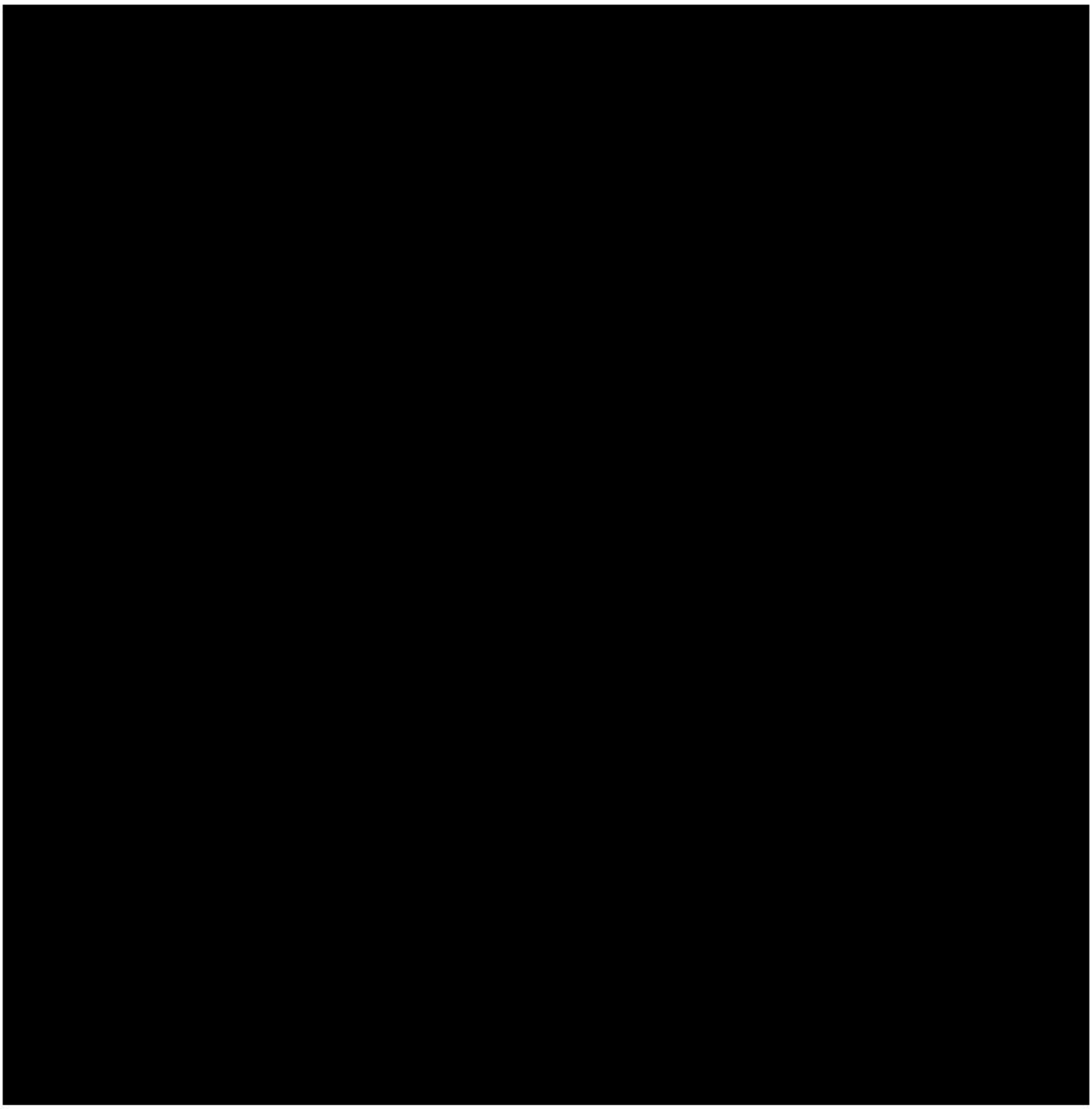
CEAP	Clinical Etiological Anatomical Pathophysiological
CRO	Contract Research Organization
CRF	Case Report Form
CVI	Chronic Venous Insufficiency
DOAC	Direct Oral Anti-Coagulant
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
DVT	Deep Venous Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
IFU	Instructions for Use
INR	International normalized ratio
IPC	Intermittent Pneumatic Compression
ISO	International Standards Organization
IVUS	Intravascular Ultrasound
NYHA	New York Heart Association
PE	Pulmonary Embolism
rVCSS	revised Venous Clinical Severity Score
RT	Reflux Time
RVF	Residual Volume Fraction
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOC	Standard of Care
USADE	Unanticipated Serious Adverse Device Effect
VFI	Venous Filling Index
VAS	Visual Analog Scale
VV	Venous Volume

20 REVISION HISTORY









21 REFERENCES

1. Maurins U, Hoffmann BH, Losch C, Jockel KH, Rabe E, Pannier F. Distribution and prevalence of reflux in the superficial and deep venous system in the general population--results from the Bonn Vein Study, Germany. Journal of vascular surgery. 2008;48(3):680-7.
2. Abramson JH, Hopp C, Epstein LM. The epidemiology of varicose veins. A survey in western Jerusalem. J Epidemiol Community Health. 1981;35(3):213-7.
3. Beaglehole R, Prior IA, Salmond CE, Davidson F. Varicose veins in the South Pacific. Int J Epidemiol. 1975;4(4):295-9.
4. Coon WW, Willis PW, 3rd, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. Circulation. 1973;48(4):839-46.
5. da Silva A, Widmer LK, Martin H, Mall T, Glaus L, Schneider M. Varicose veins and chronic venous insufficiency. Vasa. 1974;3(2):118-25.
6. Guberan E, Widmer LK, Glaus L, Muller R, Rougemont A, Da Silva A, et al. Causative factors of varicose veins: myths and facts. An epidemiological study of 610 women. Vasa. 1973;2(2):115-20.
7. Mekky S, Schilling RS, Walford J. Varicose veins in women cotton workers. An epidemiological study in England and Egypt. Br Med J. 1969;2(5657):591-5.
8. Norgren L, Widmer LK. Venous function, evaluated by foot volumetry, in patients with a previous deep venous thrombosis, treated with streptokinase. Preliminary results. Vasa. 1978;7(4):412-4.
9. Stvrtinova V, Kolesar J, Wimmer G. Prevalence of varicose veins of the lower limbs in the women working at a department store. Int Angiol. 1991;10(1):2-5.
10. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation. 2000;102(20):E126-63.
11. Van den Oever R, Hepp B, Debbaut B, Simon I. Socio-economic impact of chronic venous insufficiency. An underestimated public health problem. Int Angiol. 1998;17(3):161-7.
12. Kurz X, Kahn SR, Abenhaim L, Clement D, Norgren L, Baccaglini U, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. Int Angiol. 1999;18(2):83-102.
13. Maffei FH, Magaldi C, Pinho SZ, Lastoria S, Pinho W, Yoshida WB, et al. Varicose veins and chronic venous insufficiency in Brazil: prevalence among 1755 inhabitants of a country town. Int J Epidemiol. 1986;15(2):210-7.
14. Hume M. A venous renaissance? Journal of vascular surgery. 1992;15(6):947-51.
15. Jantet G. [The socioeconomic impact of venous pathology in Great Britain]. Phlebologie. 1992;45(4):433-7.
16. Fagrell B. Microcirculatory disturbances - the final cause for venous leg ulcers? Vasa. 1982;11(2):101-3.

17. Becker F. [Mechanisms, epidemiology and clinical evaluation of venous insufficiency of the lower limbs]. Rev Prat. 1994;44(6):726-31.

18. Becker F, Menassa M, Gabrielle F, Brenot R, David M. [What complementary examinations to demand in chronic venous insufficiency?]. Phlebologie. 1992;45(3):297-303; discussion 4-6.

19. Christopoulos DG, Nicolaides AN, Szendro G, Irvine AT, Bull ML, Eastcott HH. Air-plethysmography and the effect of elastic compression on venous hemodynamics of the leg. Journal of vascular surgery. 1987;5(1):148-59.

20. Ma H, O'Donnell TF, Jr., Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord. 2014;2(4):355-61.

21. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

22. Gloviczki P. Handbook of Venous Disorders. 3 ed: Hodder Arnold 2009.

23. Welch HJ, Faliakou EC, McLaughlin RL, Umphrey SE, Belkin M, O'Donnell TF, Jr. Comparison of descending phlebography with quantitative photoplethysmography, air plethysmography, and duplex quantitative valve closure time in assessing deep venous reflux. Journal of vascular surgery. 1992;16(6):913-9; discussion 9-20.

24. Iafrati MD, Welch H, O'Donnell TF, Belkin M, Umphrey S, McLaughlin R. Correlation of venous noninvasive tests with the Society for Vascular Surgery/International Society for Cardiovascular Surgery clinical classification of chronic venous insufficiency. Journal of vascular surgery. 1994;19(6):1001-7.

25. Weingarten MS, Branas CC, Czeredarczuk M, Schmidt JD, Wolferth CC, Jr. Distribution and quantification of venous reflux in lower extremity chronic venous stasis disease with duplex scanning. Journal of vascular surgery. 1993;18(5):753-9.

26. O'Donnell TF, Jr., Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (R) and the American Venous Forum. Journal of vascular surgery. 2014;60(2 Suppl):3S-59S.

27. Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. Journal of vascular surgery. 2010;52(5):1387-96.

28. Kahn SR, Lamping DL, Ducruet T, Arsenault L, Miron MJ, Roussin A, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. J Clin Epidemiol. 2006;59(10):1049-56.

29. McEnroe CS, O'Donnell TF, Jr., Mackey WC. Correlation of clinical findings with venous hemodynamics in 386 patients with chronic venous insufficiency. Am J Surg. 1988;156(2):148-52.

30. Fronek A. Photoplethysmography in the diagnosis of venous disease. Dermatol Surg. 1995;21(1):64-6.

31. Ishibashi H, Hayakawa N. A New Position for Photoplethysmography Assessment of Lower Leg Venous Function-Technical Notes. Int J Angiol. 1998;7(4):297-300.

32. Kurstjens RL, de Wolf MA, Alsadah SA, Arnoldussen CW, Strijkers RH, Toonder IM, et al. The value of hemodynamic measurements by air plethysmography in diagnosing venous obstruction of the lower limb. J Vasc Surg Venous Lymphat Disord. 2016;4(3):313-9.

33. Gillespie DL, Cordts PR, Hartono C, Woodson J, Obi-Tabot E, LaMorte WW, et al. The role of air plethysmography in monitoring results of venous surgery. Journal of vascular surgery. 1992;16(5):674-8.

34. Criado E, Farber MA, Marston WA, Daniel PF, Burnham CB, Keagy BA. The role of air plethysmography in the diagnosis of chronic venous insufficiency. Journal of vascular surgery. 1998;27(4):660-70.

35. Criado E, Daniel PF, Marston W, Mansfield DI, Keagy BA. Physiologic variations in lower extremity venous valvular function. Ann Vasc Surg. 1995;9(1):102-8.

36. Harada RN, Katz ML, Comerota A. A noninvasive screening test to detect "critical" deep venous reflux. Journal of vascular surgery. 1995;22(5):532-7.

37. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2014;130(4):333-46.

38. Nishibe T, Kudo F, Miyazaki K, Kondo Y, Nishibe M, Muto A, et al. Relationship between parameters of air plethysmography and types of superficial venous reflux in patients with primary varicose veins. Int Angiol. 2008;27(5):385-8.

39. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health. 1999;53(3):149-53.

40. Fowkes FG, Evans CJ, Lee AJ. Prevalence and risk factors of chronic venous insufficiency. Angiology. 2001;52 Suppl 1:S5-15.

41. Vasquez et al. Revision of the venous clinical severity score: Venous outcomes consensus statement: Special communication of the American Venous Forum Ad Hoc Outcomes Working Group. JOURNAL OF VASCULAR SURGERY. November 2010, Volume 52, Number 5

42. N. A. Goldenberg, et al. Definition of post-thrombotic syndrome following lower extremity deep venous thrombosis and standardization of outcome measurement in pediatric clinical investigations. Journal of Thrombosis and Haemostasis, 10: 477–480

43. S K van der Velden, et al. Translation and validation of the Dutch VEINES-QOL/Sym in varicose vein patients. Phlebology 2014;29 :227–235

APPENDIX A