INVESTIGATION PLAN

Investigator Initiated Safety Study Using the Venclose Vestico (commercial name TBD) Radiofrequency (RF) Ablation System for the Treatment of Incompetent Perforator Veins (IPVs)

Protocol No.: CL-VAV-001

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). All personnel involved in the conduct of this study have completed Good Clinical Practice (GCP).

Reference Documents

- Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including First in Human (FIH) Studies, Guidance for Industry and Food and Drug Administration Staff, October 1, 2013.
- Guidance for Industry, E9 Statistical Principles for Clinical Trials, FDA, 1998.
- Draft Guidance for Clinical Trial Sponsors, On the Establishment and Operation of Clinical Trial Data Monitoring Committees, FDA, 2001.
- Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice ISO 14155:2011).
- ICH GCP E6.
- U.S. CFR Title 21 Parts 50 and 56 and CFR Title 45 Part 46.
- U.S. 21 CFR 812.25 and 812.27
- Guidance for Industry and Food and Drug Administration Staff, Collection of Race and Ethnicity Data in Clinical Trials, FDA, October 26, 2016
- Guidance for Industry and Food and Drug Administration Staff, Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies, FDA, September 12, 2017

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines.

Principal Investigator and Sponsor's Point of Contact:

Signed: Signature on File Date: _____

Name: Dr. Jeffrey G. Carr
Title: Principal Investigator

Signed: Signature on File Date: _____

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Venclose, Inc.

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LIST OF ABBREVIATIONS

Term	Explanation
ABI	Ankle-Brachial Index
BMI	Body Mass Index
CEAP	Clinical-Etiology-Anatomy-Pathophysiology classification
CFR	Code of Federal Regulations
CVI	Chronic Venous Insufficiency
DUS	Duplex Ultrasound
DVT	Deep Venous Thrombosis
EC	Ethics Committee
GCP	Good Clinical Practices
GSV	Great Saphenous Vein
IPV	Incompetent Perforator Vein
IV	Intravenous
PI	Perforator Incompetency
PV	Perforator Vein
RF	Radiofrequency
RFA	Radiofrequency Ablation
SEPS	Subfascial Endoscopic Perforating Vein Surgery
SFJ	Sapheno-Femoral Junction
SPJ	Sapheno-Popliteal Junction

Section 3 – INVESTIGATION PLAN

CLINICAL PROTOCOL SUMMARY

Title:	**Investigator Initiated Safety Study Using the Venclose Vestico (commercial name TBD) Radiofrequency (RF) Ablation System for the Treatment of Incompetent Perforator Veins (IPVs)**
Synopsis:	An Investigator Initiated study conducted to evaluate the safety of the Venclose digiRF Generator with Vestico Catheter System ("Vestico") treating incompetent perforator veins (IPVs). The study will be conducted in compliance with IDE requirements under local IRB approval(s). Study data will be summarized and submitted to FDA in a premarket notification once all subjects have completed 30-day follow-up. Venclose's venous ablation technology is already cleared by FDA for use in treating chronic venous insufficiency, especially treating saphenous and branching veins, and has been in clinical practice since 2017 with extremely low adverse events. The study's working hypothesis is that using the Venclose Vestico Catheter System will safely treat incompetent perforator veins (IPVs) without resulting in any adverse outcomes related to use of the device. A physician with extensive clinical background and experience in treating vascular and venous diseases and a medical license to practice in the United States will use the Vestico device to treat a minimum of 30 IPVs on at least twenty (≥ 20) and a maximum of thirty (≤ 30) subjects.
Description of Intervention:	Following informed consent, the physician operator will gain access to the IPV in the leg using ultrasound guidance. The Vestico device will be inserted into the vein lumen also with ultrasound imaging guidance and the target treatment position confirmed. After providing local anesthesia to the vein and surrounding tissues, the Vestico device will be activated to deliver the thermal ablation energy to the vessel. Once the treatment cycle has been completed the device will be withdrawn and closure confirmed with duplex ultrasound. A bandage and compression hose will be applied. The patient will then immediately ambulate.
Number of Sites:	Single Site
Objectives:	1) The study's working hypothesis is that using the Venclose Vestico Catheter System for treating incompetent perforator veins (IPVs) will not result in significant adverse outcomes related to use of the device.

2) The study will be conducted in compliance with IDE requirements and labeling (21 CFR 812.2(b)) under local IRB approval(s).

3) Multiple limbs and IPVs may be treated. All IPVs treated will be followed according to the study schedule.

Population: At least twenty (≥ 20) and a maximum of thirty (≤ 30) ambulatory subjects diagnosed with Incompetent Perforator Veins (IPVs) who meet the inclusion and exclusion criteria, both males and females over the age of 18, will be enrolled at one clinic.

Primary Endpoints:

1) Safety - Procedure related adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), serious adverse device effects (SADE) and unanticipated adverse device effects (UADE) will be monitored 3 days, 15 days (+/- 3 days), and 30 days (+/- 3 days) post-procedure and analyzed for acceptability post study .

   Monitored events include:
   - Edema
   - Skin changes
   - Venous ulcers
   - Deep vein thrombosis
   - Superficial vein thrombosis
   - Pulmonary embolism
   - Venous thromboembolism
   - Skin burn
   - Thermal injury of adjacent tissues
   - Paresthesia
   - Infection/cellulitis
   - AV Fistula
   - Need for re-operation
   - Death

2) Effectiveness - Technical success, defined as successful access and entry into the IPV to be ablated and the ability to deliver the intended energy to the target vein segment, will be evaluated.

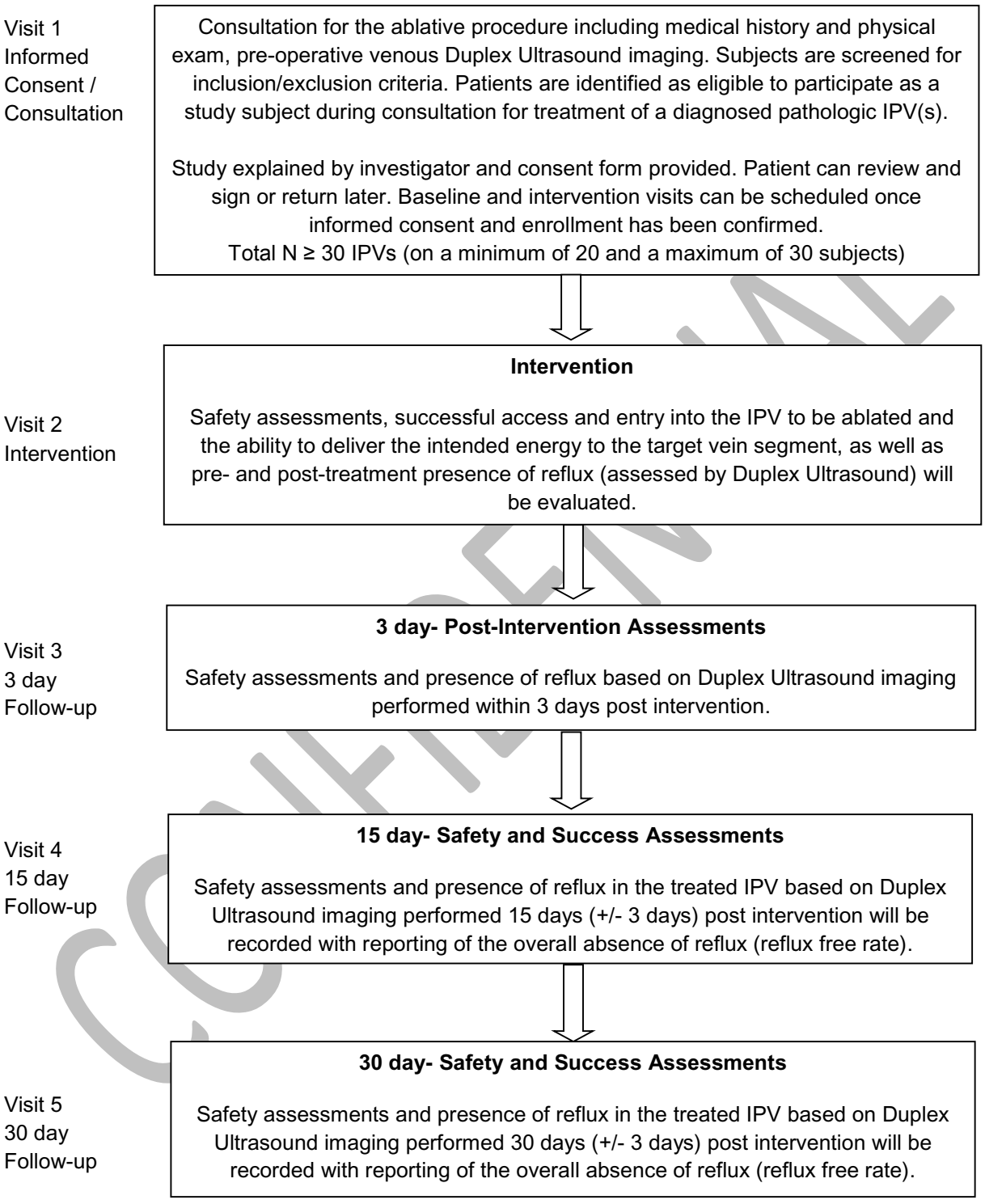
Secondary Endpoints:

1) The acute ablation success endpoint is defined as complete lack of flow or IPV disappearance in the treated segment (vessel occlusion). Success will be measured by Duplex Ultrasound imaging performed 3 days, 15 days (+/- 3 days), and 30 days (+/- 3 days) post-procedure.

2) Presence of reflux in the treated IPV will be recorded at each time point (3, 15, and 30 days post intervention) and an overall

	absence of reflux rate (i.e. reflux free rate) will be documented at each follow-up time point
Subject Participation Duration:	Five Visits: An Informed Consent / Consultation visit; Intervention visit; routine follow-up within 3 days post-intervention, follow-up visit at 15 days post-intervention, and final follow-up visit at 30 days post-intervention. Total duration: three - five hours.
Study Duration:	Three to four months

Schematic of Study Design:



1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION

2.1 Background Information

As stated by the Society of Vascular Surgery in 2011, in the Western adult population, the prevalence of varicose veins is > 20% (range, 21.8%-29.4%), with about 5% (range, 3.6%-8.6%) have advanced disease manifesting as lower extremity venous edema, skin changes or venous ulcerations. Active venous ulcers are present in up to 0.5%, and between 0.6% and 1.4% have healed ulcers. On the basis of estimates of the San Diego epidemiologic study, more than 11 million men and 22 million women between the ages of 40 and 80 years in the United States have varicose veins, and 2 million adults have advanced CVD, with skin changes or ulcers. The incidence of post-thrombotic venous ulcers has not changed in the past two decades for women, and it recently increased in men. In the United States each year, at least 25,000 patients receive a new diagnosis of venous ulcers. Chronic venous insufficiency (CVI) is prevalent worldwide.[12]

As the primary established mode of endovenous therapy for CVI in the US for over 20 years, thermal ablation for venous reflux via a time-temperature based thermal injury produces collagen denaturation and vein diameter reduction resulting in safe and efficacious fibrotic occlusion of the vessel.

Incompetent perforator vein treatment using the Venclose Vestico Catheter System uses the same mechanism of action (MOA) as the Medtronic RFS procedure cleared by FDA (K number) for IPVs as well as the same MOA as the Venclose EVSRF procedure previously cleared by the FDA (K number) for thermally ablating Saphenous reflux. The only difference between the RFS and the Vestico/EVSRF technology is the mode of thermal energy delivery which is bipolar energy delivered directly to the patient tissues for RFS vs. patient isolated resistive heating for the Vestico/EVSRF technology. Thermal energy (i.e., heat energy; time-at-temperature) is what effects successful collagen denaturation and vessel occlusion. Both bipolar and resistive technologies accomplish the same result (i.e., both impart heat energy to occlude the vessel). In the case of the Vestico system, the resistive heating technology is inherently safer since the patient (i.e., patient's tissues) is not used as part of the electrical circuit which is the case for the FDA cleared RFS device currently in use today. Additionally, resistive heating technologies like the Venclose EVSRF and Medtronic ClosureFAST technologies have proven to be the standard of care for much larger diameter vessels than required for treating perforator veins. Consequently, based on the understanding of the thermal effects on collagen, and on the typical size of the target vein anatomy, these resistive heating technologies are well-suited for successful treatment of incompetent perforators.

2.2 Study Outline

The study's working hypothesis is that using the Venclose Vestico Catheter System for treating incompetent perforator veins (IPVs) will not result in significant adverse outcomes related to use of the device.

There will be an informed consent/consultation visit and an intervention visit. A pre-operative Duplex Ultrasound imaging will be obtained prior to or during the consultation visit. The Vestico device will be used to treat IPVs during the intervention visit. Safety assessments and pre- and post-treatment Duplex Ultrasound imaging will be obtained measuring reflux during the primary intervention. Safety assessments and post-operative Duplex Ultrasound images will be obtained within 3 days after the intervention. All subjects will be followed up at 15 days and 30-days post-operatively for a safety assessment and Duplex Ultrasound. No further study intervention, study visits or study-specific data collection will follow the 30-day follow-up. The subject population will be patients in need of treatment for Chronic venous insufficiency (CVI) and disease due to IPVs.

2.2.1 Device Name

Device Trade Name: **Venclose Vestico System**
Regulation Description: Electrosurgical cutting and coagulation device and accessories
Product Code: GEI
Regulation Number: 21CFR 878.4400

2.2.2 Intended Use

The Venclose VESTICO (commercial Name TBD) Catheter is intended to be used with the Venclose digiRF Generator as a system.

2.2.3 Indication for Use

The Venclose VESTICO (commercial Name TBD) Catheter is intended for endovascular coagulation of blood vessels in patients with perforator and tributary vein reflux.

2.2.4 Device Description

The Venclose Vestico System uses resistive radiofrequency ablation (via energy delivered to heat the wall of an incompetent vein) with temperature-controlled RF energy, and an already widely accepted procedure to cause irreversible luminal occlusion. This is followed by fibrosis and ultimately resorption of the vein.

Venclose Vestico System consists of two (2) main components:

1) Vestico catheter with integrated cable connector which treats the vein in 0.5 cm segments (Figure 1) and
2) Venclose digiRF generator (model VC-RFG-1) which delivers radiofrequency (RF) energy to the Vestico catheter (digiRF generator already cleared under, K160754) (Figure 2).

Figure 1: Vestico Catheter

Figure 2: Venclose digiRF Generator

The Vestico catheter is a slight modification to the sponsor's already cleared EVSRF catheter (K160754) for the treatment of superficial veins. The primary components of the catheter, as illustrated in Figure 3, include the shaft, handle and integrated connector cable. The catheter shaft is 6 French (6F = 2.0 mm in diameter) in profile, with an insertable length of 40 cm and a 0.5 cm heating coil, which is energized by the digiRF generator. The shaft's lumen allows passage of a guidewire 0.025" or smaller in diameter to help steer the catheter into position within the vasculature, as needed.

The technology and design used in the Vestico catheter is identical to the EVSRF catheter and developed based on special considerations for human factors and usability engineering with features included to provide easy handling for the operator. The parent technology of EVSRF catheter used in Vestico with human factors testing has been reviewed and cleared by the FDA. Briefly, the catheter handle includes a manual start/stop button, the circuitry for communication with the generator, and a luer connector for flushing of the guidewire lumen prior to catheter insertion into the vein (Figure 3). The button on catheter gives full control of the device operation to the user, such as to activate or terminate treatments, or to pause and re-start as necessary.

In addition, all treatment parameters for the Vestico catheter are provided with no user-selectable adjustments. The graphical user interface uses icons and digits for readability from distances of up to eight feet away and with symbols for understanding across users with different primary languages. The procedure can be performed in an outpatient setting, without the need for general anesthesia, allowing for a walk-in/walk-out procedure with minimal post-operative recovery time.

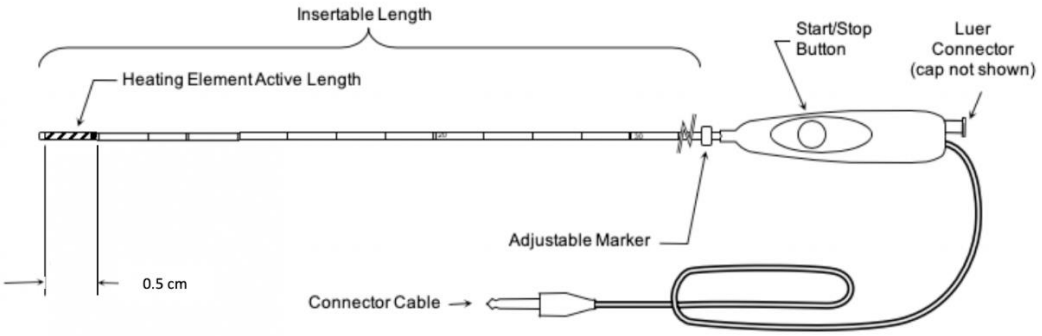

Figure 3: Vestico Catheter

The tip of the Vestico catheter where the heating coil is located is covered with a non-stick outer layer, which enables thermal control and prevents the device from tissue burns because of residual heating. The catheter is also fully shielded by several non-conductive polymer layers (including the non-stick outer jacket) to prevent delivery of electric current into patient tissues
.

2.3 Potential Risks and Benefits

The risks associated with participation in this study present no greater probability or magnitude of harm or discomfort than those ordinarily encountered as standard of care for endovenous thermal ablation.

The following explanation is offered as the rationale for this risk determination under Title 21 CFR 812.150(b)(10).

Under 21 CFR 812.3(m), a Significant Risk (SR) device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.

    - The Vestico Device is not an implant, nor does it present serious risk to the health, safety or welfare of the subject.

2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.

    - The Vestico Medical Device does not support or sustain human life.

3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

    - Vestico Device is used for treating IPVs; however, does not present a potential for serious risk to the health, safety, or welfare of a subject.

4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

    - The Vestico Device does not present a serious risk for health, safety, or welfare of a patient

In order to determine if a particular risk is considered serious, FDA guidance regarding serious adverse event was reviewed. In this guidance document, OHRP defines *serious adverse event* as any adverse event that:

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);

3. results in inpatient hospitalization or prolongation of existing hospitalization;

4. results in a persistent or significant disability/incapacity;

5. results in a congenital anomaly/birth defect; or

6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

If the Vestico Device fails, it will not lead to death, won't create a life-threatening situation, would not lead to additional patient hospitalization, would not disable the patient, and would not lead to additional surgical procedures of the patient.

2.3.1 Potential Risks

Risks from undergoing endovenous thermal ablation:

The Vestico ablation procedure will be performed by trained and registered medical doctors who follow standard of care for RFA. While thermal ablation procedures have inherent risks, problems with the procedure are considered rare, and when they do occur, they are usually minor and easily treated.

Some of the potential risks identified are:

- Edema
- Skin changes
- Venous ulcers
- Deep vein thrombosis
- Superficial vein thrombosis

- Pulmonary embolism
- Venous thromboembolism
- Skin burn
- Thermal injury of adjacent tissues
- Paresthesia
- Infection/cellulitis
- AV Fistula
- Need for re-operation
- Death

Before undergoing ablation procedure, subjects will be informed by the treating clinician of these potential side effects using the clinical informed consent form, in addition to a separate informed consent form for the research study.

Known risks from use of the subject device:

During the development of the device, a Risk Management process compliant with ISO 14971 Medical devices - Application of risk management to medical devices was undertaken. Upon completion of this process it has been determined that known device related risks that may result in patient's harm have been either mitigated or reduced to a level that is as low as reasonably possible.

The approaches followed by the sponsor to mitigate the occurrence of device related risk include designing the device for inherent safety and providing information for safety. Specific risk controls implemented to protect patients from harm are respectively described below:

- Injury to electric shock – designed the device to make it compliant with all applicable requirements regarding electrical safety as defined in IEC 60601-1 *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance*.
- Injury from sharp edges - designed the device to make it compliant with all applicable requirements regarding mechanical safety as defined in IEC 60601-1 *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance*.
- Infection due to use of contaminated patient contacting components – Single-patient use components are provided sterile while for reusable components, users are provided with cleaning and sterilization instructions which had been validated per national and international standards on reprocessing of reusable medical equipment.
- Patient contacting components provoke a biocompatibility response – designed the device to make it compliant with all applicable requirements of ISO 10993-1 *Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process*

- Training – All study investigators and their staff will receive GCP training and attend an Investigator meeting to be trained on the study protocol and procedures. Prior to use, clinicians and assistants receive training according to the commercial training program on the use of the Vestico Device and all of its components.

Duplex Ultrasound:

Duplex ultrasound is a non-invasive evaluation of blood flow through the arteries and veins. This test provides information to help the vascular interventionist make a sound diagnosis and outline an appropriate treatment plan. Accuracy is critical, so ultrasound testing should be performed by a credentialed sonographer in an experienced vascular laboratory. There are typically no side effects or complications associated with duplex ultrasound examinations.

Pregnant women, children and adolescents have been excluded from the study.

2.3.2 Potential Benefits to Subjects

From undergoing ablation procedures:

There are several potential benefits to patients undergoing thermal ablation therapy to IPVs including some or all of the following: Partial or complete (active) ulcer healing, reduced likelihood of ulcer recurrence, pain reduction at the site of or adjacent to the active or healed ulcer, prevention or reduction of complications from untreated or undertreated vein leg ulcers such as infections (cellulitis, phlebitis, osteomyelitis, sepsis), hospitalizations, minor or major leg or foot amputations and death. Other potential health benefits included reduction in edema, focal pain at the site of active skin changes and inflammation, and improved appearance and health of the skin in the legs. In addition there are potential non-medical benefits to the patients which include reduction in extended wound care visits and therapies, travel costs and time to multiple doctor or care providers visits, time away from work and loss of income for the patient and/or primary caretakers, costs of medications and supplies, side effects from medications, potential for opiate addiction due to relief of chronic pain and mental distress from a chronic medical problem.

2.3.3 Alternatives to Participation

Participation is voluntary. Alternatives to vein leg ulcer therapy include non-operative management including compression garment therapy (graduated hose, stockings, pneumatic pumps, etc.), leg elevation, and exercise. Although these are important as adjunctive therapies, they are overall ineffective at healing active ulcers in a timely fashion. Other interventional treatments include surgical therapy such as SEPS (subfascial endoscopic perforator surgery) which is more invasive

and rarely utilized, thermal ablation therapy with a laser or radiofrequency device, and ultrasound-guided foam sclerotherapy. These techniques have technical and efficacy challenges due to the variances and complexities of perforator anatomy.

CLINICAL PROTOCOL

A study conducted to evaluate the safety and effectiveness of the Venclose digiRF Generator with Vestico Catheter System ("Vestico") treating incompetent perforator veins (IPVs). The study will be conducted in compliance with IDE requirements under local IRB approval(s). Study data will be summarized and submitted to FDA in a premarket notification once all subjects have completed 30-day follow-up.

The study working hypothesis is that using the Venclose Vestico Catheter System for treating incompetent perforator veins (IPVs) will not result in any adverse outcomes related to use of the device.

No significant risk is posed by either the use of the Vestico Device or the study process. While safety can never be taken lightly, this study is not meant to measure, monitor or analyze any significant disease or disorder for which medical treatment is mandatory.

3 OBJECTIVES

3.1 Study Objectives and Outcome Measures

Objectives

1) The study's working hypothesis is that using the Venclose Vestico Catheter System for treating incompetent perforator veins (IPVs) will not result in significant adverse outcomes related to use of the device.

2) The study will be conducted in compliance with IDE requirements and labeling (21 CFR 812.2(b)) and under local IRB approval(s).

3) Multiple limbs and IPVs may be treated. All IPVs treated will be followed according to the study schedule.

Outcome Measures

Primary Endpoints:

1) Safety - Procedure related adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), serious adverse device effects (SADE) and unanticipated adverse device effects (UADE) will be monitored and analyzed for acceptability post study.

   Monitored events include:
   - Edema
   - Skin changes
   - Venous ulcers
   - Deep vein thrombosis
   - Superficial vein thrombosis
   - Pulmonary embolism
   - Venous thromboembolism
   - Skin burn
   - Thermal injury of adjacent tissues
   - Paresthesia
   - Infection/cellulitis
   - AV Fistula
   - Need for re-operation
   - Death

2) Effectiveness - Technical success, defined as successful access and entry into the IPV to be ablated and the ability to deliver the intended energy to the target vein segment, will be evaluated.

Secondary Endpoints:

1) The acute ablation success endpoint is defined as complete lack of flow or IPV disappearance in the treated segment (vessel occlusion). Success will be measured by Duplex Ultrasound imaging performed 3 days, 15 days (+/- 3 days), and), and 30 days (+/- 3 days) post-procedure.

2) Presence of reflux in the treated IPV will be recorded at each time point (3, 15, and 30 days post intervention) and an overall absence of reflux rate (i.e. reflux free rate) will be documented at each follow-up time point

3.2 Overview

A. Subjects

At least twenty (≥ 20) and a maximum of thirty (≤ 30) subjects eligible for endovenous thermal ablation, specifically IPVs, will be enrolled in this study.

B. Protocol

i. Enrollment: At least twenty (≥ 20) and a maximum of thirty (≤ 30) subjects requiring thermal ablation will be asked to participate in this study. Exclusion criteria will include any factors excluding a patient from having RFA (e.g. medical conditions, psychological conditions, or vascular conditions) and/or exclude the use of the Vestico Device (See Section 4 for detailed inclusion/exclusion criteria).

ii. Clinical Procedures: There will be an informed consent/consultation visit and an intervention visit. A pre-operative Duplex Ultrasound imaging will be obtained prior to or during the consultation visit. The Vestico device will be used to treat IPVs during the intervention visit. Safety assessments and pre- and post-treatment Duplex Ultrasound imaging will be obtained measuring reflux during the primary intervention. Safety assessments and post-operative Duplex Ultrasound images will be obtained within 3 days after the intervention. All subjects will be followed up at 3-days, 15-days and 30-days post-operatively for a safety assessment and Duplex Ultrasound. No further study intervention, study visits or study-specific data collection will follow the 30-day follow-up. The subject population will be patients in need of treatment for Chronic venous insufficiency (CVI) and disease due to IPVs.

iii. The Investigator proceeds with the Vestico Device procedure and will take a post-operative Duplex Ultrasound Scan following the ablation procedure.

iv. Data and Imaging Collection and Study Monitoring: On the day of surgery, Screening and Baseline Visit Case Report Forms (CRFs) will be completed by the Investigator or their delegate. The clinical study monitor will confirm that Pre- and Post-Operative Duplex Ultrasound Scans are taken.

v. Analysis: The treatment plan, including the pre-operative Duplex Ultrasound Scan, and post-operative Duplex Ultrasound Scan images are collected by the clinical study monitor. Cessation of flow and cessation of flow reflux through the perforator vein(s) will be recorded, thoroughly investigated, documented and included in the study analysis. All adverse events related to the device will be handled and reported to regulatory authorities as per this study protocol.

D. Data Collection

Data will be collected using case report forms (CRFs). The following describes the data being collected:

- Imaging and surgical preplanning information
- De-identified subject data (e.g. age, gender, medications and medical conditions)
- Device related data
- Surgical site data (e.g. location), blood flow, etc.
- Surgical Information (date and reason for the surgery, complications)
- Duplex Ultrasound Scans from pre- and immediately post-intervention.
- All adverse events

E. Investigators

One investigator with a wide range of endovascular interventional experience and his assistants will be trained on the protocol, investigator and sponsor responsibilities, study procedures and the instructions for use of the Vestico device. (See Appendix A). The investigators and staff will be certified with GCP training.

A qualified clinical study monitor will verify data collection.

F. Oversight (see Section 15.2, Institutional Review Board)

This study will be subjected to review by an Institutional Review Board in addition to the oversight provided by the principal investigator and the clinical study monitor to ensure that the rights, welfare and safety of subjects are protected.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Patient is >= 18 years.
2. IPVs to be treated have an outward flow duration of >= 0.5 seconds immediately after release of manual distal compression with patient standing or in Reverse Trendelenburg.
3. IPV(s) to be treated have a diameter of ≥ 3.5 mm located caudal edge of ankle.
4. Has been diagnosed with refractory symptomatic disease attributable to the IPV to be treated.
5. Is able to ambulate.
6. Is able to comprehend and has signed the Informed Consent Form (ICF) to participate in the study.
7. Is willing and able to comply with the Clinical Investigation Plan and follow-up schedule.

4.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Has venous insufficiency secondary to venous obstruction proximal to the intended treatment site.
2. Has thrombus in the vein segment to be treated.
3. Has untreated critical limb ischemia from peripheral arterial disease.
4. Is undergoing active anticoagulant therapy for Deep Vein Thrombosis or other conditions (e.g., warfarin, direct oral anticoagulant or low molecular weight heparin) or has a history of Deep Vein Thrombosis within the last 6 months or hypercoagulable state.
5. Patients with known bleeding or clotting disorders or unwilling or unable to frequently ambulate post-operatively.
6. Has had prior venous procedures in the study limb within the last 30 days (including thrombolysis, thrombectomy, stenting, ablation, phlebectomy, visual or foam sclerotherapy).
7. Has undergone or is expected to undergo any major surgery within 30 days prior to or following the study procedure.
8. Has a condition, judged by the treating physician, that may jeopardize the patient's well-being and/or confound the results or the soundness of the study.

9. Is pregnant or lactating at the time of the study procedure or is intending on becoming pregnant within 30 days following the study procedure.
10. Is participating in another clinical study that is contraindicated to the treatment or outcomes of this investigation

4.3 Strategies for Recruitment and Retention

At least twenty (≥ 20) and a maximum of thirty (≤ 30) subjects who desire treatment for their varicose veins will be recruited and enrolled from one clinical site. Study advertising in the form of an accredited IRB approved flyer will be posted in each clinic in high visibility areas as necessary. Patients interested in obtaining further information will be invited to inquire at the clinic reception to receive study information and arrange for the consent process to be started. Patients who are being consulted for treatment of varicose veins may also be informed by their attending physician that the study is taking place. Recruitment and screening efforts will continue until the target number of subjects has been reached.

4.4 Subject Withdrawal

Since final follow-up will be at 30 days post-intervention, it is unlikely subjects will withdraw from the study. However, subjects may withdraw voluntarily from the study or the investigator may terminate a subject's participation at any time. Withdrawals will be reported to an accredited IRB. In the case of a withdrawal of an enrolled subject, a new subject will be enrolled in order to reach the target enrollment of a minimum of thirty (≥ 30) IPVs across at least twenty (≥ 20) and a maximum of thirty (≤ 30) subjects.

4.4.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon his or her request without prejudice to medical care. An investigator has a duty to terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.4.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

Subjects who are removed from the study as a result of clinical conditions during surgery that prevent implant placement will be included in the study analysis of data. For the purposes of analyzing accuracy, it will be necessary to enroll another implant patient so that study results are not affected.

Subjects may be removed from the study at their request. In the event that a subject wants to be withdrawn from the study, reasonable effort will be made to ascertain the reason for the withdrawal which will be documented in the subject's CRF. However, the study subject is not obligated to provide a reason for their withdrawal. In the case of a withdrawal of an enrolled subject, a new subject will be enrolled in order to reach the target enrollment.

4.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause as described in the circumstances below. If the study is prematurely terminated or suspended, the principal investigator will promptly inform FDA and the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5 STUDY INTERVENTION

5.1 Concomitant Medications/Treatments

All concomitant medications will be recorded on a study CRF for each subject. The information about these medications will be collected and recorded prior to enrollment. If subjects are enrolled on a date prior to the ablation procedure, the concomitant medications will be reviewed and updated with the subject for accuracy during the first study visit and prior to the surgical intervention utilizing the Vestico Device.

5.2 Administration of Intervention

The Vestico device will be utilized during the RFA at the one clinic in the United States and the intervention will be performed by the qualified study investigators trained in the use of the Vestico device. This intervention will occur at one visit only and should take approximately two hours.

5.3 Accountability Procedures for the Study Product

The sponsor, Venclose, Inc., will supply the Vestico Devices to the clinical site at no charge. Supply of the consumable (Vestico Catheter) and reusable (Vestico Generator) components will also be provided at no charge in sufficient quantity to meet the requirements of the study.

The study CRFs include capture of serial, batch/lot numbers of components used for each study subject. These will be compared to unused and returned supply at study close to ensure that each consumable and reusable component is accounted for.

5.3.1 Deficient Product

If a device deficiency is detected, the investigator will discontinue use of the affected component and report this deficiency immediately to the study sponsor.

The study sponsor will investigate and determine corrective or preventive actions if required.

Additional supplies may be requested in writing to the study sponsor if deficiencies require replacement of the device or its consumable or reusable components.

5.4 Procedures for Training Investigators and Study Monitoring

Investigators will have documented certification of GCP training.

Investigators will receive practical training for the Vestico Device that will be conducted by qualified Venclose training personnel according to Venclose's approved customer training procedure. Prior to site initiation, training of the investigators and assistants will be provided by the sponsor and Principal Investigator and will cover the following: study protocol, Investigator

and Sponsor responsibilities, and site procedures. A follow up training session to review these materials will be conducted at site initiation by the clinical study monitor and Venclose Training personnel. Training records will be created for each trainee.

Only registered investigators and assistants who have documented training in GCP, have received the required study related training, and are determined to be proficient in the use of the Vestico device will participate in the conduct of the study.

A qualified clinical study monitor will verify collection of data, and monitor compliance to the protocol and study procedures. The monitor is required to report any deviations from the site procedures or study protocol to the sponsor and Principal Investigator.

Venclose Service and Support technicians may be on-site to provide technical support to the clinician, should they request it. The Service and Support personnel will not be involved in the planning or be present in the operatory during the procedure to ensure that data recorded is not compromised.

6 STUDY PROCEDURES

6.1 Subject Recruitment

Potential study subjects may be identified through in-clinic advertising in the form of a flyer posted in high visibility areas. Interested potential participants may approach clinic staff to express their interest and receive Informed Consent information. Patients who are being consulted for treatment of their varicose veins may also be informed by their attending physician that the study is taking place and if interested, an Informed Consent appointment can be booked with the Investigator or his/her designate.

6.2 Informed Consent

The informed consent visit will be conducted by the Investigator or their designated study staff at the time of the consultation for intervention visit and may occur up to one month before the scheduled intervention.

- Review all aspects of the clinical investigation that are relevant to the possible subject's decision to participate
- Care is to be taken not to coerce or unduly influence possible subject participation
- Provide ample time for the possible subject to read and understand the informed consent form and to consider participation
- Answer all questions asked to the satisfaction of the possible subject
- Provide a copy of the signed informed consent to the possible subject, if signed
- Arrange for Screening / Enrollment Visit

A copy of the IRB approved Informed Consent Form is located in Appendix B of this document.

6.3 Costs to Subjects and Payment for Participation

There will be no cost to subjects as a result of participating in this study. Participants will receive a $75-$150 pre-loaded gift card for each completed study visit to cover travel and out-of-pocket expenses related to the study.

6.4 Consultation / Enrollment

Consultation Visit (up to two months before the scheduled intervention)

- Confirm documented informed consent from potential subject
- Obtain/review medical/clinical history (standard of care)
- Assess/review eligibility based on inclusion/exclusion criteria
- Review concomitant medications history to determine eligibility based on inclusion/exclusion criteria (standard of care)

- Perform medical/clinical examinations needed to determine eligibility (standard of care)
- Obtain demographic information (standard of care)
- Determine surgical site(s)
- Pre-operative Duplex Ultrasound Scan
- Schedule study intervention visit for individuals who are eligible and available for the study (standard of care)
- Complete Screening CRF
- Provide potential subjects with instructions and possible prescriptions needed to prepare for the intervention visit (standard of care)

6.5 Baseline / Intervention

Baseline Visit (Day of intervention)

- Verify inclusion/exclusion criteria
- Review concomitant medications (standard of care)
- Record results of physical and clinical examinations (standard of care)
- Complete Baseline CRFs
- Perform ablation procedure (standard of care) using the Vestico Device
- Post-operative Duplex Ultrasound Scan (same day and within 3 days of Intervention)
- Record AEs and SAEs and report to sponsor immediately (if applicable)

6.6 3-day Post-Intervention Safety Assessment

Follow-up Visit (3-days post-intervention)

- Document all adverse events, if any
- Post-operative Duplex Ultrasound Scan (same day or within 3 days of 3-day Follow-up)

6.7 15-day Post-Intervention Safety Assessment

Follow-up Visit (15-days post-intervention)

- Document all adverse events, if any
- Post-operative Duplex Ultrasound Scan (same day or within 3 days of 15-day Follow-up)

6.8 30-day Post-Intervention Safety Assessment

Follow-up Visit (30-days post-intervention)

- Document all adverse events, if any

- Post-operative Duplex Ultrasound Scan (same day or within 3 days of 30-day Follow-up)

6.9 Withdrawal Visit

Any subjects wishing to withdraw or be withdrawn by the clinician will be scheduled for a withdrawal visit. Reasonable efforts will be made to ascertain the reason for withdrawal which will be documented in the subject's CRF. However, the study subject is not obligated to provide a reason for their withdrawal. Withdrawals will be reported to an accredited IRB per their guidelines.

6.10 Unscheduled Visit

Subjects in need of a visit between the screening and baseline visits will be scheduled and any treatment or evaluation will be documented in a study CRF if they have not completed the baseline visit.

7 STUDY SITE SELECTION

7.1 Site Selection

Site will be selected based on the following criteria:

i. Geographic location;
ii. Expertise in therapeutic area;
iii. Level of experience and training (clinic, research, etc.);
iv. Availability of appropriate type and number of subjects;
v. Adequate facilities, staff, resources; including an on-site Duplex Ultrasound Scanner;
vi. No undisclosed financial or professional conflict of interest with the proposed study; and
vii. The investigator is not the subject of current investigation or review by their licensing organization or other regulatory body.

8 ASSESSMENT OF SAFETY

8.1 Reporting Procedures

8.1.1 Reportable Events and Unanticipated Problems, Reporting to FDA and IRB

A reportable event is defined as anything that could significantly impact the conduct of the research or alter the Institutional Review Board's (IRB) approval or favorable opinion to continue the research.

An unanticipated problem is defined as any incident, experience, or outcome (including an adverse event) that meets all of the following criteria:

- **Event is unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as this IRB approved research protocol and informed consent document, or the Device Instructions for Use; (b) the event is not associated with the expected natural progression of any underlying disease, disorder, predisposing risk factor, or condition of the participant(s) experiencing the adverse event; and

- **Related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the investigational product(s) or procedure involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Should an unanticipated problem, or reportable event occur due to participation in this study, the information will be recorded in the subject CRFs and reviewed by the sponsor.

Adverse Events or Serious Adverse Events that are Unanticipated Problems

NOTE: Report to the IRB only adverse events that in the opinion of the investigator may represent unanticipated problems involving risks to the other subjects in the research.

The investigator must immediately inform the sponsor of any unanticipated problems, adverse events and/or serious adverse events. The investigator is responsible for reporting adverse events without delay to the IRB that fit the above criteria.

8.2 Time Period and Frequency for Event Assessment and Follow-Up

Any unanticipated problems, adverse events and/or serious adverse events will be recorded in the subject CRF during the study. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of the study participation. The investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9 STUDY OVERSIGHT

In addition to the responsibility of the principal investigator to oversee study conduct, an independent clinical study monitor will conduct routine monitoring visits to minimize the instances of errors or missing data, to provide assurance that the study documentation is completed according to procedures and to assess compliance with the protocol, GCPs and intended use of the device. (See section 11.)

10 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by a qualified individual independent of the study. The monitor will evaluate study processes and documentation based on International Conference on Harmonization (ICH), E6: Good Clinical Practice guidelines (GCP).

Some monitoring activities may be performed remotely, while others will take place at the study site(s). The independent monitor will conduct monitoring activities and provide reports of the findings and associated action items to the site study team, the study PI and the sponsor. The clinical study monitor will conduct routine monitoring visits and will verify the collection of required data elements. Additional monitoring will be done at the discretion of the Sponsor and clinical study monitor.

11 ANALYTICAL METHODS

11.1 Data Analysis

Appropriate analytical methods will be used to interpret the study results. Techniques may include:

- Descriptive statistics and graphical plots (i.e., box and whisker plots) to assess the central tendency and variability of the raw data
- Distribution diagnostics and outlier test to determine degree of nonlinearity and other systematic error. All missing data will be assumed to be missing-at-random, unless trends are detected.
- Any statistical analysis will be performed using JMP Statistical Software, Version 15.0 (SAS Institute Inc., Cary, NC.)

11.2 Lost to Follow-up

Data on subjects who are lost to follow-up or who withdraw from the study will be maintained and analyzed up to the point at which they discontinued. The reason for withdrawal will be recorded if known. Subjects who discontinue participation, for whatever reason, will remain in the study and be subject to follow-up in the same manner as those who complete the study except as noted above. The only confirmed lost to follow-up subject will be the subject who dies or refuses to continue to participate in the study and withdraws.

11.3 Sample Size Estimate

This is an Investigator Initiated Study; there is no formal sample size calculation. A minimum of thirty (≥ 30) IPVs on at least twenty (≥ 20) and a maximum of thirty (≤ 30) subjects will be enrolled.

1) Along with the available Real-World Evidence data, the number of IPVs proposed is satisfactory compared with number of IPVs used in other early studies performed for "Substantial Equivalence" 510k pathways requiring human data in the field of thermal ablation for venous reflux.

2) Based on Real World Evidence and MAUDE database review, the number of AEs and MDRs, respectively, is very low. If a study is designed to evaluate what is already observed in RWE, it would drive sample sizes for statistical justification to be extremely high, which is overly burdensome to demonstrate "substantial equivalence".

3) Based on review of the technical features of the predicate device vs. subject device, the set-point temperature and thermal ablation size are "substantially equivalent". This means the thermal spread is the same providing reasonable level of assurance of safety and effectiveness. The proposed sample size for this study is large enough to understand any differences in performance between subject and predicate devices.

4) Post-hoc review of the study results will be performed on any AEs and/or occlusion data to determine if results provide an acceptable level of substantial equivalence.

DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

Study staff will maintain appropriate clinical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

12 QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA) PROCEDURES

12.1 Quality Management System

The sponsor, Venclose, Inc. maintains a quality system that is Certified to ISO 13485 CMDCAS and ISO 9001 standards and is in compliance with FDA ‘s 21 CFR 820, *Medical Device Regulation*. Clinical Quality Assurance and Quality Control will be integrated in the sponsor’s overall quality system and will be overseen by the Sponsor’s Department of Quality Assurance and Regulatory Affairs. All members of this department have received training and certification in GCP by an accredited GCP training institution.

12.2 Clinical Quality

The sponsor maintains written Clinical Quality procedures for the design, conduct and monitoring of clinical studies. This includes written procedures to ensure that trials are conducted and data are generated, recorded and reported in compliance with the approved study protocol, GCP and applicable regulatory requirements.

For activities related to the use of the subject device in the Clinical study, the sponsor’s established Quality Management System procedures will be utilized e.g. Quality System Procedures for Adverse Event Reporting and Corrective and Preventive Action.

12.3 Study Conduct and Agreements

A written Clinical Trial Agreement (CTA) between and among the Institution, Principal Investigator and the sponsor includes agreement to allow direct access to all trial related sites, source data/documents, and reports for the purposes of monitoring and auditing by the sponsor, as well as for inspection by domestic and foreign regulatory authorities.

12.4 Quality Control

The sponsor employs a clinical study monitor who is responsible for overseeing the progress, conduct, records and reporting in accordance with the protocol, SOPs, GCP and other identified regulatory requirements. The activities of the monitor are documented in the sponsor’s SOP for Clinical Study Monitoring. The sponsor assures that the monitor is appropriately trained to perform these activities. Training is documented according to QSP 6.2-1. (See section 6.4.).

The study CRFs and regulatory files will be reviewed for verification and agreement to the study protocol by the Clinical Monitor, Principal Investigator, and the sponsor’s Quality Assurance and Regulatory Affairs Department.

12.5 Essential Documents

The quality management of essential documents (i.e. CRFs, informed consent forms; refer to Section 8 of the ICH for a complete list of documents) will be conducted by the clinical study monitor with oversight of the Principal Investigator.

12.6 Study Data

The sponsor will be provided de-identified data only.

The sponsor's document control coordinator is responsible for the quality management of subject/participant data (study CRFs and de-identified radiographs). Once the sponsor has received these documents from the site(s), the clinical study monitor initiates an internal review by the sponsor's Quality Assurance and Regulatory Affairs department to ensure that records are accurate, complete, legible and timely. Any data queries that result from this review must be resolved. The Principal Investigator must review and approve each study CRF that has been completed by investigator(s) before the data can be used.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki and The Belmont Report: “Ethical Principles and Guidelines for the Protection of Human Subjects of Research”, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

13.2 Institutional Review Board (IRB)

The protocol and informed consent form will be submitted to an accredited IRB for review and approval prior to beginning the study and before enrolling subjects. Any amendment to the protocol will require review and approval by an accredited IRB before the changes are implemented in the study.

The IRB, in addition to the oversight provided by the principal investigator and the clinical study monitor, serves to ensure that the rights, welfare, and safety of patients is protected.

13.3 Informed Consent Process

A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be approved by an accredited IRB.

The subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to consider the risks and benefits prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

13.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals, 18 years and older, of any gender or racial/ethnic group may participate. Pregnant women will be excluded. Children are excluded from the study as they are still developing and are typically not candidates for this procedure.

13.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. At the time of screening and enrollment, study subjects will be assigned a

unique subject ID which will be used for study documentation. Personal information collected for study purposes will be identified only by their assigned subject ID. The screening and enrollment log will be held in electronic form on a password protected and secured server and maintained by the Principal Investigator. The personal identification of study subjects will be accessible only by the PI and will not be shared with the sponsor. Study records are retained according to ICH and FDA guidelines.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third-party without prior written approval of the sponsor.

The clinical study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

14 DATA HANDLING AND RECORD RETENTION / KEEPING

The investigators are responsible for ensuring the data reported is attributable, legible, contemporaneous, original and accurate (ALCOA). All source documents are to be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation. All original study CRFs and de-identified scans will be securely transferred to and maintained by the sponsor via Venclose personnel or insured parcel service (requiring receipt signature). Records will be stored in locked boxes in secure, fire-safe cabinets accessible only to authorized study team members.

The sponsor will retain original records related to the study for at least two years after the last subject's study visit date. Some examples of study records include device use instructions, all versions of the protocol and informed consents, CRFs etc.

14.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff and clinical study monitor under the supervision of the investigator and study sponsor. The study sponsor maintains policies and procedures to support the generation of high-quality, reliable, and statistically sound data and results from the study.

De-identified data from paper CRFs and accuracy measurements taken from radiographs will be transcribed by qualified individuals into a validated study database developed and maintained by the study sponsor. All data will be verified for accuracy and reconciled by the sponsor's quality assurance team.

14.2 Data Capture Methods

All data will be captured on paper study CRFs. All original CRFs will be transferred to the sponsor via insured parcel service (requiring receipt signature), within seven days of completion of each subject's study participation. A copy of these documents will be maintained at the study site until the sponsor has verified receipt of the original documents. Once the sponsor confirms receipt of the originals, a site study team member will be instructed by the sponsor to destroy the CRF copy (e.g. shred).

Shipment of documents to sponsor will occur as follows:

John J. Carlow, EdD, MPH
Discovery Statistics
31434 West Nine Drive
Laguna Niguel, CA. 92677

14.3 Study Records Retention

Study records will be retained by the sponsor per the sponsor's Clinical Quality procedures.

14.4 Protocol Deviations

All deviations from the protocol must be addressed in study subject source documents and promptly reported to an accredited IRB, according to their requirements.

15 PUBLICATION / DATA SHARING

The Investigator may not publish or otherwise disseminate the results of its investigative findings without written authorization of the Sponsor.

APPENDIX A: TRAINING GUIDE AND CHECKLIST

APPENDIX B: INFORMED CONSENT FORM