LIBERTY 360°: Prospective, Observational, Multi-Center Clinical Study to Evaluate Acute and Long Term Clinical and Economic Outcomes of Endovascular Device Intervention in Patients with Distal Outflow Peripheral Arterial Disease (PAD)

NCT 01855412

[redacted]

21-August-2014

Sponsor:

Cardiovascular Systems, Inc.

[redacted]

PROTOCOL SUMMARY

Title	**LIBERTY 360:** Prospective, Observational, Multi-Center Clinical Study to Evaluate Acute and Long Term Clinical and Economic Outcomes of Endovascular Device Intervention in Patients with Distal Outflow Peripheral Arterial Disease (PAD).	
Study Design	Prospective, observational, multi-center clinical study to evaluate endovascular device interventions in treating lower extremity PAD with critical limb ischemia (CLI) and/or intermittent claudication.	
Study Purpose	The purpose of this study is to evaluate acute and long term clinical and economic outcomes of procedures to treat PAD.	
Study Population	Patients with symptomatic lower extremity PAD that requires endovascular device intervention and includes at least one target lesion in a native vessel located within or extending into 10 cm above the medial epicondyle to the digital arteries.	
Study Sample Size	Approximately 1,200 subjects to be enrolled at up to 100 U.S. sites: • Up to 500 subjects - "Claudicant" Arm (Rutherford 2-3) • Up to 600 subjects - "CLI Rutherford 4-5" Arm • At least 100 subjects - "CLI Rutherford 6" Arm	
Primary Objectives	The objectives of this study are: 1. Evaluate procedural and long-term clinical and economic outcomes for subjects undergoing peripheral endovascular device intervention of lower extremity PAD that includes a target lesion in a native vessel located within or extending into 10 cm above the medial epicondyle to the digital arteries. [redacted]	
Follow-Up Visits	All subjects will be followed post-procedure to discharge; at 30 days ±15 days; at 6 and 18 months ±30 days; 12 and 24 months ± 60 days and annually (± 60) thereafter until completion of the 5-year post-treatment follow-up or study termination; whichever occurs first.	
Study Endpoints	Various endpoint measures will be collected and assessed: 1. Procedural and lesion success 2. Rate of major adverse events (MAEs): o Death within 30 days of index procedure o Unplanned major (above the ankle) amputation of the target limb o Clinically-driven TLR and/or TVR of the target limb [redacted]	
Sponsor Contact Information	Cardiovascular Systems, Inc. (CSI) [redacted]	
Primary Investigator(s) Contact Information	"Claudicant" Arm (Rutherford 2-3)	William Gray, MD Columbia University Medical Center [redacted]
	"CLI Rutherford 4-5" Arm	Gary Ansel, MD Riverside Methodist Hospital [redacted] George Adams, MD Rex Healthcare [redacted]
	"CLI Rutherford 6" Arm	Jihad Mustapha, MD Metro Health Hospital [redacted]

Angiographic Core Lab	SynvaCor/Prairie Educational and Research Cooperative (PERC) [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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1. ABBREVIATIONS

[redacted]	[redacted]
ABI	Ankle Brachial Index
AE	Adverse Event
AT	Anterior Tibial
BA	Balloon Angioplasty
CFR	Code of Federal Regulations
CLI	Critical Limb Ischemia
CSI	Cardiovascular Systems, Inc.
[redacted]	[redacted]
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IC	Intermittent Claudication
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
MAE	Major Adverse Event
LER	Lower Extremity Revascularization
OAS	Orbital Atherectomy System
PAD	Peripheral Artery Disease
PI	Principal Investigator
POBA	Plain Old Balloon Angioplasty
POP	Popliteal
PPG	Photoplethysmography
PR	Peroneal Tibial
PT	Posterior Tibial
PTA	Percutaneous Transluminal Angioplasty
[redacted]	[redacted]
SFA	Superficial Femoral Artery
TBI	Toe Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
TPT	Tibial Peroneal Trunk
US	United States
[redacted]	[redacted]

2. DEFINITIONS

Term	Definition
Dissection classification[1]	Type 0: None Type A: Small radiolucent area within lumen of the vessel Type B: Linear, non-persisting extravasation of contrast Type C: Extraluminal, persisting extravasation of contrast Type D: Spiral shaped filling defect Type E: Persistent lumen defect with delayed ante/retrograde flow Type F: Filling defect accompanied by total arterial occlusion *Note: Type A and B are generally considered benign and minor dissections.*
Digital arteries	Arteries that are the collateral digital branches of the dorsal metatarsal arteries in the foot.
Outflow	Arterial flow to the foot starting from tibial vessels (AT, TPT, PT, and PR arteries).
Inflow	For the LIBERTY study, inflow treatment on the target limb is defined as treatment located entirely above the protocol defined target area, not inclusive of any lesion that extends into the target area, as defined by the LIBERTY protocol.
Lesion success (per lesion)	A final post-procedural result of < 50% residual stenosis for a given target lesion treated during index procedure as determined by the Angiographic Core Laboratory without significant angiographic complications.
[redacted]	[redacted]
Major adverse events (MAEs)	Death within 30 days of index procedure, unplanned major (above ankle) amputation of index limb, clinically-driven target lesion revascularization (TLR) or target vessel revascularization (TVR) of the index limb.
Procedural success (per subject)	A final post-procedural result of < 50% residual stenosis for all treated target lesions during index procedure without significant angiographic complications, as determined by the Angiographic Core Laboratory.
Rutherford classification[2]	**Class 0**: Asymptomatic; no hemodynamically significant occlusive disease. **Class 1**: Mild Claudication; there is no limitation with ordinary physical activities (e.g., walking several blocks, climbing stairs). Limiting symptoms may occur with marked exertion (e.g., strenuous, rapid or prolonged exertion at work or recreation). **Class 2**: Moderate Claudication; there is a slight limitation of ordinary physical activities (e.g., walking uphill, or more than two level blocks, or climbing stairs rapidly). Patient is comfortable at rest. **Class 3**: Severe Claudication; there is marked limitation of ordinary physical activities (e.g., walking 1-2 level blocks or climbing one flight of stairs). Patient is comfortable at rest. **Class 4**: Ischemic rest pain. **Class 5**: Minor tissue loss, non-healing ulcer, focal gangrene with diffuse pedal ischemia. **Class 6**: Major tissue loss extending above transmetatarsal level; functional foot no longer salvageable.
Significant Angiographic complications	Perforation, dissection type C-F, distal embolization, acute vessel closure that occurred during index treatment of target lesion(s).
Target area	An area located within or extending into10 cm above the medial epicondyle to the digital arteries.
Target lesion(s)	Stenotic segment(s) within or extending into the target area treated with an endovascular device(s) during the index procedure.
Target lesion revascularization (TLR)	Repeat revascularization of the target lesion(s) includes: • Percutaneous transluminal angioplasty (PTA) • Stenting • Atherectomy • Bypass graft • Other treatments

Term	Definition
Target vessel revascularization (TVR)	Repeat revascularization of the target vessel(s) (exclusive of the target lesion) includes: • PTA • Stenting • Atherectomy • Bypass graft • Other treatments

3. INTRODUCTION

The prevalence and economic impact of peripheral artery disease (PAD), a widespread public health concern, continues to rise in conjunction with a growing elderly population, as well as with increasing rates of diabetes. In 2001, in the United States (US) alone, PAD affected 8-12 million patients and was associated with significant morbidity and mortality.[3] The current amputation rate in the US is approximately 160,000 US patients per year.[4] Of note, recent studies document that more than 50% of these patients at risk for amputation never undergo an arterial evaluation prior to amputation.[5] This is of particular interest since minimally invasive endovascular therapies for PAD have been developed and are available for clinical use. Thus, additional evidence-based trials on these new endovascular devices are needed, not only to improve awareness, but to improve clinical outcome of patients with severe PAD.

Current medical treatment guidelines recommend supervised exercise and phosphodiesterase inhibitor (cilostazol) in patients with symptomatic PAD (intermittent claudication), but in clinical practice these treatments are difficult to implement. Supervised exercise therapy for PAD is currently not reimbursed by Medicare and studies have shown that patients find it difficult to follow an exercise regimen on their own.[6] In addition to exercise, patients without heart failure may be treated with cilostazol which promotes symptomatic improvement in walking distance,[7] but this medical therapy is often limited because the drug is restricted to patients without heart failure and many patients experience intolerable side effects. Previously, when medical management failed, surgical bypass of the affected arteries was previously the only available option for revascularization and historically was reserved for patients with critical limb ischemia (CLI), a more common form of limb-threatening PAD.

Development of novel endovascular techniques and devices such as balloon angioplasty, stenting, and atherectomy, now provides viable non-surgical, minimally invasive treatment options for many patients with PAD. Minimally invasive endovascular therapy offers inherent advantages over traditional surgical revascularization, such as lower morbidity, shorter hospital length of stay, and considerably less patient discomfort. As the field of endovascular therapy continues to grow, the need for traditional surgical therapies will be considerably reduced.[8] Over the past decade there has been an exponential rise in lower extremity percutaneous peripheral intervention with a concomitant drop in surgical intervention.[9] Specifically, the national per capita (100,000 population, age > 40 years) volume of major amputations decreased by 38%.

The volume for national use of endovascular lower extremity revascularization doubled. The volume of open lower extremity revascularization decreased by 67% from 1998 through 2007. Interventions declined by 20% (93 to 75) for critical limb ischemia (CLI) but increased by nearly 50% for claudication. Outpatient data analysis revealed a fivefold increase in vascular interventions for CLI and claudication. Nationally, endovascular LER interventions quadrupled (8% to 32%) for CLI and doubled (26% to 61%) for claudication.[10] Another study using a Nationwide Inpatient Sample from 1996-2005 analyzed 97,000 acute admissions for PAD, 83,000 major amputations, 77,500 endovascular procedures, and 171,000 open vascular bypass operations. Between 1996 and 2005, population-based rates of acute admissions for PAD decreased by 4.3% per year, open procedures by 6.6% per year, and major amputations by 6.4% per year, whereas endovascular procedures increased by 4.8% per year.[11]

As endovascular options for PAD patients continue to expand, choice of revascularization must be considered in the context of the patient's clinical status, specific anatomic and lesion characteristics, and the optimal device features to ensure success. Well-designed and executed investigations that track clinically relevant outcomes, including the cost of the endovascular treatments and long term outcomes will enable physicians to determine the optimal therapies for patients with PAD. This will ultimately advance both treatments and outcomes for PAD patients.

4. DEVICES USED IN STUDY

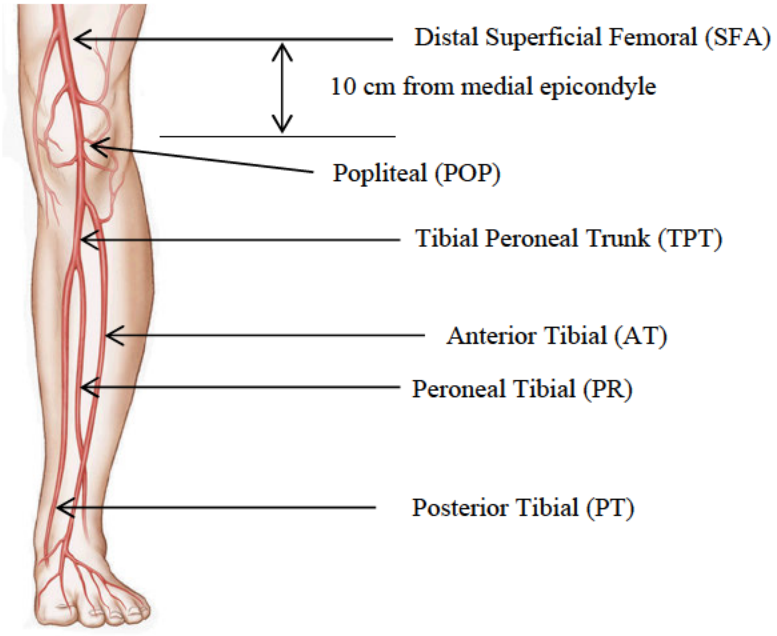
This clinical study is designed to collect observational clinical data for all subjects with distal outflow PAD who are suitable for endovascular device intervention. Only endovascular devices cleared or approved for commercial use by the Food and Drug Administration (FDA) can be used in this study. Please refer to the appropriate device-specific Instructions for Use (IFU). There will be no investigational devices allowed in this study.

5. STUDY DESIGN AND STATISTICAL METHODOLOGY

5.1. STUDY DESIGN

This is a prospective, observational, multi-center, clinical study examining predictors of clinical outcomes for patients undergoing endovascular treatment of lesions within or extending into the target area (10 cm above the medial epicondyle to the digital arteries). This includes disease in a vessel located within or extending into the distal superficial femoral artery (SFA), popliteal (POP), tibial peroneal trunk (TPT), anterior tibial (AT), posterior tibial (PT), and peroneal tibial (PR) arteries (see Figure 1).

Figure 1: Treatment Locations



5.2. STATISTICAL METHODOLOGY

This observational study will analyze the outcome measures based on outlined endpoints. The study data will be reported using descriptive analysis.

6. SAMPLE SIZE AND SUBJECT ENROLLMENT

6.1. SAMPLE SIZE

Approximately 1,200 subjects will be enrolled in this study. The study cohort will be divided into three study arms according to the most severe clinical syndrome present at the time of study enrollment:

- "Claudicant" Arm (Rutherford 2-3) – up to 500 subjects
- "CLI Rutherford 4-5" Arm – up to 600 subjects
- "CLI Rutherford 6" Arm – at least 100 subjects

Based on a unique study design that includes all commercially available endovascular treatment options for lower extremity PAD, the Sponsor will stop the study enrollment once goals for the study are met. However, since the study may be conducted in up to 100 sites in U.S., there may be some subjects enrolled at the same time at multiple sites leading to an overall study cohort exceeding 1,200 subjects.

6.2. SUBJECT ENROLLMENT

The subject will be considered enrolled in the study when:

- He/she signs an informed consent form (ICF);
- All of the inclusion and none of the exclusion criteria are met; and,
- At least one lesion in the target area of a native vessel is treated with an endovascular device.

  Note: a) at least one target lesion must be crossed and treated for subject to be considered enrolled in the study.

  b) if during index procedure, endovascular treatment of the target lesion is converted to bypass, subject is not considered enrolled in the study, therefore no study follow-up is needed.

All efforts will be made to ensure that consecutive subjects are being included in the study. The subject's treatment method(s) will be determined by the treating Investigator. Assignment to study arms will be based upon Rutherford classification at baseline

[redacted]

6.3. SUBJECT SELECTION

Subjects must meet ALL of the inclusion criteria and NONE of the exclusion criteria to be eligible to participate in this study.

6.4. INCLUSION CRITERIA

1. Subject's age ≥ 18 years.
2. Subject presents with a Rutherford classification of 2 to 6.
3. Subject presents with clinical evidence of PAD requiring endovascular intervention on one or both limbs that includes a target lesion in a native vessel located within or extending into 10

cm above the medial epicondyle to the digital arteries.
- If subject presents with bilateral disease, the first limb treated with a lesion in the target area will be considered the target limb.
- For subjects with one or more wounds on the target limb, the target lesion(s) should be considered the lesion(s) in the vessel(s) that provide(s) blood flow to the wound(s).

4. Subject has at least one lesion in a native vessel located within or extending into the target area that is crossed and treated with an endovascular device.
   Note: the Investigator can make an additional attempt to treat a lesion in the target area at a later time point if the initial attempt to treat was unsuccessful. If successful on re-intervention, the subject can be enrolled.

6.5. EXCLUSION CRITERIA

1. Subject is unwilling or unable to sign the IRB-approved informed consent form (ICF).
2. Subject is unable to understand or comply with the study protocol requirements.
3. Subject is currently participating in an investigational drug or other device study that can clinically interfere with the endpoints of this study.
4. Subject requires a conversion from endovascular intervention to a surgical bypass graft for any lesion(s) in the target area, as determined by the Investigator.
5. Subject has an in-stent restenosis in the target area, and this lesion is the only one requiring treatment.
6. Subject is pregnant or planning to become pregnant within the study period.
7. Subject has an anticipated life span of less than one (1) year.

7. STUDY OBJECTIVE

The objectives of this study are:

1. Evaluate procedural and long-term clinical and economic outcomes for subjects undergoing peripheral endovascular device intervention used to treat lower extremity PAD that includes a target lesion in a native vessel located within or extending into the target area (10 cm above the medial epicondyle to the digital arteries). This includes disease in the distal SFA, POP, TPT, AT, PT, and PR arteries.

[redacted]

8. STUDY ENDPOINTS

All study endpoints will be assessed by the study treatment group that will include Rutherford classification and type of intervention.

Endpoint 1: Procedural and Lesion Success
Procedural success is defined as a final post-procedural result of < 50% residual stenosis for all treated lesions during the index procedure and without significant angiographic complications, (perforation, dissection type C-F, distal embolization, acute vessel closure) as determined by the Angiographic Core Laboratory.

Lesion success is defined as a final post-procedural result of < 50% residual stenosis for a given lesion treated during the index procedure and without significant angiographic complications, as determined by the Angiographic Core Laboratory.

Endpoint 2: Rate of Major Adverse Events (MAEs)

The rate of the following MAEs as reported by the Investigators will be assessed during the subject's participation in the study:

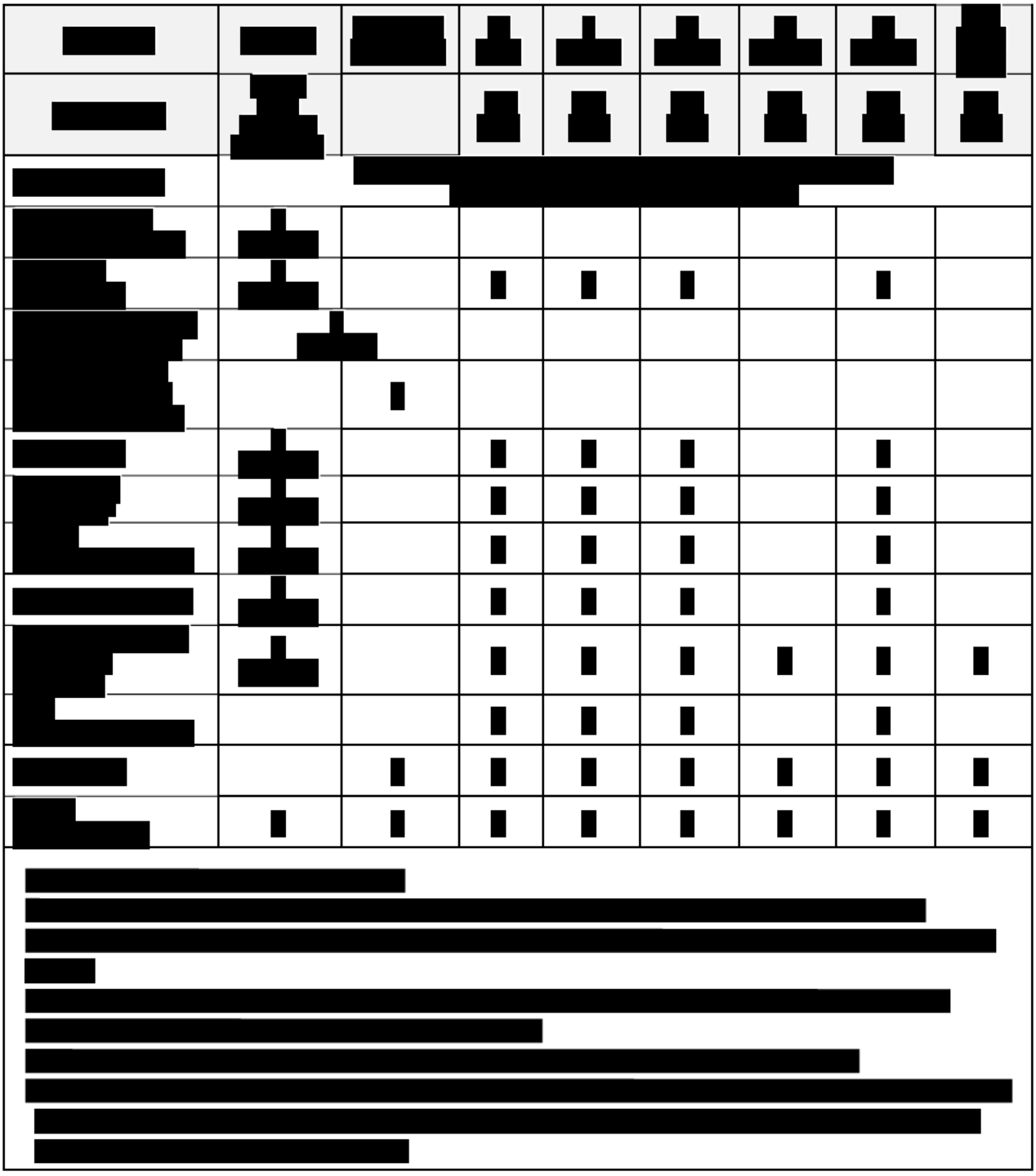
- Death within 30 days of index procedure
- Unplanned major (above the ankle) amputation of the target limb
- Clinically-driven TLR and/or TVR of the target limb

[redacted]

9. FOLLOW-UP VISITS

All subjects will be followed post-procedure to discharge, at 30 days ±15 days; at 6 and 18 months ± 30 days; at 12 and 24 months ±60 days; and annually (±60 days) thereafter until completion of the 5-year post-treatment follow-up or study termination; whichever occurs first. Follow-up visit windows will be calculated from the date of treatment of the index lesion(s) of the target limb. [redacted]

[redacted]



11. ADVERSE EVENTS

11.1. ADVERSE EVENT DEFINITIONS

Adverse events (AEs) collected in this study will be limited to death, serious injury, angiographic complications related to the index procedure, revascularizations, amputations of either lower limb, myocardial infarction and stroke. For the purposes of this study, pre-planned interventions noted at baseline are not considered AEs.

- **Major adverse events (MAEs)** are defined for the purpose of the data analyses of the study endpoints and include:
  - Death within 30 days of index procedure
  - Unplanned major (above the ankle) amputation of the target limb
  - Clinically-driven TLR and/or TVR of the target limb

[redacted]

- **Device-related serious injuries**, including death, are required by the FDA to be reported as part of post market surveillance of medical devices per 21 Code of Federal Regulations (CFR) 803. Serious injury means an injury or illness that is device related and includes the following:
  - Is life-threatening,
  - Results in permanent impairment of a body function or permanent damage to a body structure, or
  - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

  Device related means related to any interventional device used during index procedure on the target limb.
  Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.
  Medical interventions may include hospitalizations or prolonged hospitalizations due to the use of the interventional devices used in this study.

- **Procedural angiographic events** that occur during index procedure on the target limb regardless of device relatedness that include the following:
  - Dissections of target lesion
  - Perforations of target lesion
  - Slow flow/no re-flow
  - Acute vessel closure
  - Distal embolization
  - Thrombus formation
  - Other angiographic complications determined reportable by treating physician

- **Revascularization or amputation of either lower limb** that occurs during subject's participation in the study

- **Myocardial Infarction** that occurs within 30 days following enrollment

- **Stroke** that occurs within 30 days following enrollment

- **Death** (all causes) throughout study participation

11.2. ADVERSE EVENT CLASSIFICATION

The relatedness of the AE to the treatment device(s) and procedure(s), index limb, and target lesion will be classified by the Investigator and reviewed by the Sponsor. The Investigator will use the following definitions in classifying the relationship of the AE:

- **Device Related:** AE is directly related to the device(s) used in treatment of the lesion.
- **Procedure Related:** AE is directly attributable to the index procedure.
- **Limb Related:** AE is related to the index limb.
- **Lesion Related:** AE is related to the target lesion.

11.3. ADVERSE EVENT REPORTING

Adverse events defined in section 11.1 must be reported to the Sponsor on the AE electronic case report form (eCRF) as well as the reviewing IRB, if applicable. AE information must be collected up until each subject's completion of the study. In the case of death or serious injury, Investigator must report to Sponsor as soon as possible but within 10 business days after first learning of the event.

[redacted]

13. RISKS AND BENEFITS

13.1. RISKS

All devices that will be used in this study have been cleared or approved by FDA. Clinical risks to subjects enrolled in this study are the same risks encountered if treated outside of the study. The choice of treatment for enrolled subjects will be determined by the Investigator. The Investigator should refer to the manufacturer's IFU for each technology used in the study for specific device related risks, contraindications, restrictions, warnings and precautions.

Since this study will enroll subjects who otherwise would be indicated for treatment, the pre-procedure preparation and follow-up care will be the same and do not present different risks from those not participating in the study. Some subjects may undergo additional tests per the Investigator's discretion if he/she desires to track the subject's disease state more closely.

13.2. BENEFITS

Subject's participation in this study is voluntary. There is no direct additional benefit to subjects enrolled in the study. However, information gathered from this study may help increase the understanding of the clinical and economic outcomes of endovascular treatment of claudication and CLI in patients with lower extremity PAD. These data may lead to expanded national PAD registries and help to standardize PAD definition and treatment guidelines. Ultimately, this knowledge can inform future PAD clinical trials, provide data to help physicians choose the best care for patients, and advance the treatment of lower extremity PAD.

14.PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the study is not conducted according to the protocol, FDA regulations 21 CFR Parts 50 and 56, and requirements imposed by the reviewing IRB. Protocol deviations that will be collected include, but are not limited to the following:

- Failure to obtain informed consent
- Enrolling a subject who did not meet inclusion criteria, or met exclusion criteria
- Not completing protocol-required examinations or evaluations

[redacted]

15.SITE NON-COMPLIANCE

If excessive protocol deviations are noted, the Sponsor reserves the right to suspend study enrollment until a sufficient system is in place at the site to reduce further deviations, or withdraw the site from participation in the study.

16.SUBJECT STUDY EXIT

Subjects will be followed until completion of the study or death, whichever comes first. [redacted] Reasons for exiting the study include, but are not limited to, subject lost to follow-up, subject's request to withdraw from the study, or subject death.

17.STUDY MANAGEMENT

This study will be conducted in accordance with the FDA requirements set forth in 21 CFR Parts 50 and 56.

[redacted]

17.3. EARLY TERMINATION OF STUDY

The Sponsor may terminate this observational study at any time due to the following reasons, but not limited to: low subject recruitment/enrollment, competing studies and financial reasons. Appropriate notification will be provided to all participating Investigators.

18. DATA ANALYSIS

Study data will be analyzed as indicated in the Data Analysis Plan.

18.1. ELECTRONIC DATA COLLECTION

All study data will be collected using a database located on a secure server. Electronic CRFs will be utilized where possible. The study data will be reviewed by the Sponsor and queries will be generated to clarify data as necessary.

[redacted]

19. ADMINISTRATIVE RESPONSIBILITIES

19.1. INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

Principal Investigators must submit the study protocol to their respective IRB and obtain IRB written approval before being allowed to conduct the study. Each Principal Investigator must submit to the Sponsor a signed copy of the IRB approval letter, specific to this protocol and addressed to the Principal Investigator, certifying study approval prior to enrolling subjects into the study. The Principal Investigator is also responsible for fulfilling any conditions of approval imposed by their IRB, including maintaining continuation of the approval during the entire study period. The Principal Investigator will provide the Sponsor with copies of such approvals. The Principal Investigator must also keep on file all study-related correspondence with the IRB.

19.2. INFORMED CONSENT FORM (ICF) APPROVAL

The Sponsor will provide a template ICF to each site for IRB submission prior to site initiation. This template may be modified to suit the requirements of the individual study site. The Sponsor must

pre-approve all changes to the ICF prior to initial submission to the IRB. A copy of the original IRB-approved ICF must be sent to the Sponsor prior to study start while the original must be retained at the study site. If the ICF is amended by the reviewing IRB, a copy of the approved document must be provided to the Sponsor prior to enrollment of subjects in the study.

The Investigator or authorized designee must administer the approved ICF to each prospective study subject. Informed consent must be obtained in accordance with the applicable guidelines of 21 CFR Part 50 and local laws and regulations, whichever represents the greater protection of the individual.

This study will be registered on http://www.ClinicalTrials.gov. The following statement will be included in the ICF for the study to notify the prospective subjects for the study: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

19.3. CONFIDENTIALITY

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this data will be used in a manner without identifiable reference to the subject. The Investigator consents to visits by the Sponsor or designee and authorized governmental body to review the study subjects' medical records, including any test or laboratory data that may have been recorded on diagnostic test media (e.g., angiogram).

19.4. SPONSOR RESPONSIBILITIES

Sponsor responsibilities include but are not limited to:

- Selection of Principal Investigators, study sites, and Core Laboratories who participate in the study;
- Training of participating study sites including the Investigator and staff conducting the study;
- Providing financial support to each study site which is fair, reasonable, and equitable to fair market value;
- Following/promoting all applicable regulatory standards per applicable regulations at each study site; and,
- Ownership and control of the use of data, including review and approval of study-related publications/presentations, etc.

19.5. INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the following:

- Protecting the rights, safety, and welfare of subjects.
- Conducting the investigation in accordance with the Clinical Trial Agreement with the Sponsor, the Protocol, applicable FDA regulations, including 21 CFR Part 50 and 56, and any conditions of approval imposed by the IRB.
- Delegation of study-related tasks to qualified personnel under their supervision as may be applicable; however, the Principal Investigator remains responsible for the proper conduct of the clinical study.
- Enrollment will commence when the Sponsor has received all required documentation, including but not limited to the signed Clinical Trial Agreement and IRB approvals.
- At each site, appropriate procedures must be followed to maintain subject confidentiality according to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining

appropriate approvals, consents, or releases of medical information as dictated by their site's relevant patient privacy laws.

- The study is not transferable to other sites attended by the Principal Investigator unless prior approval is obtained from the appropriate IRB and the Sponsor.
- It is recommended that all records pertaining to this study will be kept for a minimum of two (2) years following the date on which the study is completed or terminated.

20. INVESTIGATOR RECORDS AND REPORTS

20.1. INVESTIGATOR RECORDS

Investigator is responsible for preparing and/or retaining the following records:

- Subject's case history records, including: signed/dated ICF, observations of adverse events, relevant medical history, results of tests and/or exams performed in this study, and dates and data collected at office visits and telephone follow-up;
- Protocol and any amendments; and
- IRB approval documents and related correspondence.

20.2. INVESTIGATOR REPORTS

The Investigator is responsible for the preparation and submission to the Sponsor all eCRFs, AEs related to the treatment device(s) or index procedure, serious injuries, and deviations from the protocol. If any action is taken by an IRB with respect to the study, the information must be forwarded to the Sponsor in a timely manner.

[redacted]

[redacted]

21. PUBLICATION OF STUDY DATA

Any previously unpublished information provided to the Investigator by the Sponsor, such as patent applications, manufacturing processes and basic scientific data, is considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the Sponsor's written consent.

A complete manuscript describing the results of this study is considered the primary publication for the study.

[redacted]

[redacted]

22. REFERENCES

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