Feasibility Clinical Trial of the Cardio Flow FreedomFlow™ Orbital Atherectomy System to Treat Peripheral Artery Disease (FAST Trial)

Protocol Number:	010-031
Version	6.0
Date	November 20, 2017
Investigational Product	Cardio Flow FreedomFlow™ Orbital Atherectomy System
Regulatory Status	Limited to Investigational Use Only
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Duplex Ultrasound Core Laboratory	Massachusetts General Hospital The Vascular Ultrasound Core Laboratory One Bowdoin Square, 10th Floor Boston, Massachusetts 02114

This study will be conducted in compliance with Food and Drug Administration (FDA) Regulations, 21 CFR Parts 50, 54, 56, 812, and 11.

Protocol Review and Approval Page

STUDY TITLE: **Feasibility Clinical Trial of the Cardio Flow FreedomFlow™ Orbital Atherectomy System to Treat Peripheral Artery Disease (FAST Trial)**

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PROTOCOL VERSION: 6.0

PROTOCOL DATE: November 20, 2017

Investigator's Statement: I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study or protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to await IRB approval for the protocol and informed consent before initiating the study, to obtain informed consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare annual, final, and adverse event reports as required by this protocol, and to maintain study documentation for the period of time required.

Investigator Name and Signature **Name:** _____ **Signature:** _____	**Date of Signature:**
Site Name and Address:	

Protocol Synopsis

Protocol Number and Version Number	010-031, Version 6.0
Protocol Title	Feasibility Clinical Trial of the Cardio Flow **F**reedomFlow™ Orbital **A**therectomy **S**ystem to **T**reat Peripheral Artery Disease (FAST Trial)
Investigational Product	Cardio Flow FreedomFlow™ Orbital Atherectomy System • CM1001 – Control Module • H4001 –User Handle + Tubing Set
Study Objective:	To evaluate first-in-human safety and effectiveness of the Cardio Flow FreedomFlow™ Orbital Atherectomy System for atherosclerotic plaque removal in *de novo* native target lesions in the peripheral vasculature of the lower extremities.
Study Design:	Prospective, 2-centers, non-randomized single-arm study
Enrollment Size and Number of Sites:	Up to 10 subjects at up to 2 sites in the United States.
Primary Safety Endpoint:	Freedom from a composite of new on-set major adverse events (MAE) at 30-day follow-up as adjudicated by an Independent Clinical Events Adjudicator. The components of the MAE are defined as: ▪ **Cardiovascular related death:** All cardiovascular cause mortality. ▪ **Myocardial infarction (MI):** Any newly diagnosed MI post procedure, defined as CK-MB ≥2X upper limit normal (ULN). ▪ **Clinically driven target lesion revascularization (TLR):** any repeat percutaneous or surgical intervention to treat objectively documented symptoms of recurrent ischemia attributable to the treated lesion. ▪ **Clinically significant target vessel dissection:** NHLBI grade C or greater as confirmed by angiography. ▪ **Clinically significant target vessel perforation:** NHLBI Type III as confirmed by angiography. ▪ **Unplanned major target limb amputation:** Amputation of the transmetatarsals or higher that was not previously planned as part of the overall treatment strategy. ▪ **Clinically relevant distal embolization:** Emboli requiring surgical or medical intervention and/or the presence of symptoms. ▪ **Pseudoaneurysm:** disruption of the arterial wall at the treatment site as confirmed by angiography.
Secondary Safety Endpoints:	• Hemoglobin, hematocrit, and free hemoglobin (pre-and post-procedure and pre-discharge) • Device and procedure related serious adverse events at 30 days and 6 months
Primary Effectiveness:	• Technical Success, defined as the ability of the Cardio Flow FreedomFlow™ Orbital Atherectomy System to achieve a residual diameter stenosis ≤50% post treatment without adjunctive therapy, as assessed by an Angiographic Core Laboratory.
Secondary Effectiveness:	• Clinical Success, defined as the ability of the Cardio Flow FreedomFlow™

	Orbital Atherectomy System to achieve a final residual diameter stenosis ≤50% with adjunctive therapy, determined by independent angiographic core laboratory.
	• Procedure Success, defined as:
	  ○ No procedure-related MAE
	  ○ ≤ 50% residual stenosis at target lesion
	  ○ No device malfunction causing the procedure to be aborted
	• Percent of device run time less than 3 minutes cumulative total
	• Maximum balloon inflation pressure of the adjunctive plain balloon angioplasty and/or drug coated balloon angioplasty
	• Improvement of ABIs at 30 days and 6 months
	• Improvement of Rutherford Classification at 30 days and 6 months
	• Improvement of patient reported outcomes (PRO, VascuQoL questionnaire) at 30 days and 6 months
	• Clinical driven target lesion revascularization (TLR), target vessel revascularization (TVR) at 30 days and 6 months (to be evaluated by angiographic core laboratory)
	• Primary patency, primary assisted patency and secondary patency at 30 days and 6 months. Doppler ultrasound examinations at 30 days and 6 months to confirm patency (to be evaluated by duplex ultrasound core laboratory). The restenosis is defined as peak systolic velocity ratio (PSVR) of 2.5.

Inclusion Criteria:	*Subjects must meet all of the following criteria to be eligible for participation in the study:* *Inclusion Criteria* 1. Age ≥ 18 years old. 2. Subject is a candidate for percutaneous endovascular intervention for peripheral vascular disease in the lower extremity. 3. Disease is located in the common femoral, superficial femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery in arteries. 4. Objective hemodynamic criteria that subject has a resting ankle-brachial index (ABI) ≤ 0.90, OR subjects with non- compressible arteries (ABI>1.1) must have a toe-brachial index (TBI) of ≤ 0.80. 5. Clinical presentation of lifestyle limiting claudication or rest pain as characterized by Rutherford Classification 2, 3, 4, or 5. 6. Subject has de novo target lesion(s) or lesion(s) treated by percutaneous transluminal angioplasty (PTA) only greater than 3 months prior with stenosis ≥70% by visual estimation in the common femoral, superficial femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery. Up to three lesions can be treated at the index procedure provided the cumulative total lesion length is ≤ 30 cm AND all lesions are in the same leg. 7. Target reference vessel diameter (proximal to and distal to target lesion) is 2 to 5mm by angiographic visual estimation. 8. At least one patent vessel run-off to the ankle or foot at baseline. 9. The target lesion(s) can be successfully crossed with a commercially available 0.014" atherectomy guidewire without any complications during wiring

	procedure. 10. Subject signs a written Informed Consent form to participate in the study, prior to any study mandated determinations or procedure.
Exclusion Criteria:	*Subject must be excluded from participation in this study if any of the following criteria are met:* <u>*Exclusion Criteria*</u> 1. Is female with childbearing potential not taking adequate contraceptives or is currently breastfeeding. 2. Target lesion is within a native graft or synthetic graft. 3. Target lesion is an in-stent restenosis. 4. Chronic total occlusion (CTO) with wire crossed near the advential junction. 5. Subject has significant stenosis or occlusion of inflow tract (upstream disease) not successfully treated during the index procedure and prior to treatment of the target lesion. 6. History of an endovascular procedure or open vascular surgery on the index limb within 30 days prior to the index procedure. 7. Planned endovascular or surgical procedure within 30 days after the index procedure. 8. Signs and symptoms of systemic infection (temperature of ≥ 38.0° Celsius and/or WBC of ≥ 12,000 cells/μL) at the time of assessment; *Note: If infection is adequately treated and controlled (temperature < 38.0° C and WBC < 12,000 cells/μL) patient may be enrolled*. 9. Unstable coronary artery disease or other comorbid condition(s) that, in the judgment of the physician precludes safe percutaneous intervention. 10. Significant acute or chronic kidney disease with a creatinine level > 2.5mg/dL and/or requiring dialysis. 11. Evidence or history of intracranial or gastrointestinal bleeding, intracranial aneurysm, myocardial infarction or stoke within 2 months of index procedure. 12. Evidence or history of aneurysmal target vessel. 13. Clinical/angiographic evidence of distal embolization. 14. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 15. Subjects in whom anti-platelet, anticoagulant, or thrombolytic therapy is contraindicated. 16. Heparin-induced thrombocytopenia (HIT) not able to use Bivalirudin. 17. Uncorrectable bleeding diathesis, platelet dysfunction, thrombocytopenia with platelet count less than 125,000/mm2, known coagulopathy, or INR > 1.5. 18. Thrombolytic therapy within 2 weeks of the index procedure. 19. Intra-operative (intra-procedure) clinical or angiographic complication (other than non-flow limiting dissections) attributed to the use of a currently marketed device prior to introduction of the Cardio Flow atherectomy driveshaft. 20. Has life expectancy < 12 months. 21. Subject is unwilling or unable to comply with the follow-up study requirements. 22. Is currently participating in an investigational drug or another device study.

	23. Has one or more stents in the treatment vessel. 24. Lacking capacity to provide consent.
Study Duration / Follow-up Period:	Approximately 2 months enrollment period with observation periods at time of procedure, 30 days post procedure and 6 months post procedure. An interim report will be prepared after 30-day follow-up of all subjects. A final report will be prepared following completion of 6-month follow-up of all subjects. Subjects will be followed per protocol and institutional standard of care for atherectomy treatment of PAD.
Analysis Population	The primary analysis will be based on the intent-to-treat (ITT) population.

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1 BACKGROUND AND RATIONALE

Atherosclerosis causes symptomatic disease primarily in the coronary arteries, the peripheral arteries of the lower extremities, and the extra-cranial carotid arteries.[1] Of the three, peripheral artery disease (PAD) is probably the most under-diagnosed and least aggressively managed, despite its strong association with cardiovascular disease (CVD) and death. PAD is chronic occlusive artery disease of the lower extremities and a strong surrogate marker for atherosclerosis in the heart, kidneys, and brain.[1,3,4,5] PAD is associated with a 60% incidence of coronary or cerebrovascular disease.[6] About 90% of patients with symptomatic PAD have coronary artery disease (CAD) as well.[7] The disease can have devastating effects on quality of life and survival, with mortality around 30% in 5 years, 50% in 10 years and 75% in 15 years.[8] Overall, CVD causes death in 75% of PAD patients.

Most common among elderly people, diabetics, and smokers, PAD afflicts an estimated 8-12 million people in the United States alone. Its prevalence is likely to increase greatly in the next several decades as the risk factors of diabetes, smoking, hypertension, dyslipidemia and cardiovascular incidence increase.

Classic symptoms of PAD include intermittent claudication (IC), defined as leg muscle pain or weakness that occurs during walking and subsides with rest.[2] The exercise-induced symptoms are distal to the obstruction in the artery that supplies the leg. Rest pain in the toes or foot indicates that arterial blood flow cannot meet the needs of resting metabolism. The resulting critical limb ischemia (CLI) can progress to ulceration or gangrene in the toes, ankle, heel, or leg, often necessitating amputation.2

Even asymptomatic PAD patients, those without IC, have poor physical function.[9] Detecting asymptomatic PAD requires measuring and calculating the ankle/brachial index (ABI), obtained by dividing blood pressure measured in the ankle by the blood pressure measured in the upper arm.[10] In a healthy person, the ABI is 0.9 to 1.2. An ABI under 0.9 is 95% sensitive and 99% specific for the diagnosis of PAD. The lower the ABI level, the more serious is the ischemia. An ABI of 0.5 is associated with a 63% five-year survival rate, and ABIs between 0.25 and 0.4 are often associated with rest pain and tissue loss.[11] Patients with normal ABIs and IC are advised to undergo an exercise ABI assessment.[5] Patients with calcified, relatively incompressible arteries from diabetes or renal disease may have false normal ABIs. To diagnose such patients, vascular laboratories can measure a toe/brachial index or do other noninvasive testing. Physicians can also use an exercise ABI measurement to assess IC patients with normal ABI scores.[12, 13]

The overall goals of PAD treatment are to maintain or improve function, reduce or eliminate ischemic symptoms and prevent disease progression.[2] Current treatments include exercise, medical treatment to lower cholesterol and blood pressure, and surgery or percutaneous interventions to restore blood flow in patients with intermittent claudication (IC) or critical limb ischemia (CLI).[14] Invasive treatments include bypass surgery, percutaneous transluminal angioplasty (PTA)[15], percutaneous atherectomy (directional or rotational)[16], endarterectomy, excimer laser combined with PTA[17] and stenting (drug-eluting stents) of the occluded or stenosed vessel. Therapeutic angiogenesis, which uses angiogenic growth factors or bone marrow mononuclear cell therapy to stimulate growth of new blood vessels[18], and subintimal

angioplasty, in which a new lumen is tunneled between the intima and the media, are under study.[19, 20]

Technical challenges involved in treating PAD surgically or percutaneously arise from anatomy, co-existing diseases such as diabetes, restenosis, inflammation and disease progression. Surgery[21] or percutaneous interventions[22] in the aorto-iliac arteries have better results than in the femoropopliteal arteries, and in turn, results in the femoropopliteal arteries tend to be better than those in the smaller lower-leg arteries.

Atherectomy is a minimally invasive endovascular technique for removing atherosclerotic plaque from blood vessels within the body. There are three main types of atherectomy devices: directional, laser, and rotational, which includes a subset known as orbital. The current U.S. Food and Drug Administration (FDA) cleared devices for peripheral atherectomy include the SilverHawk™, TurboElite™, Rotoblator™, Diamondback™, JetStream™, Phoenix™, and Pantheris™. Cardio Flow, Inc. has pioneered advances in orbital atherectomy technology for the intravascular treatment of PAD using the Cardio Flow FreedomFlow™ Orbital Atherectomy System.

The Cardio Flow FreedomFlow™ Orbital Atherectomy System is intended to remove fibrous and calcified stenotic plaque using diamond-coated eccentric spheres attached to a driveshaft in a spiral configuration. The device intended to operate over a commercially available 0.014' atherectomy guidewire to treat vessels from 2mm to 5mm in diameter. No driveshaft lubricant is required for use with the Cardio Flow FreedomFlow™ Orbital Atherectomy System.

One GLP-like porcine studies (2 pigs) were conducted to assess safety and device performance in normal peripheral arteries a range of vessel sizes. Devices were operated according to the Instruction for Use. Animals were survived for three days post-treatment and the treated vessels were harvested and histopathological evaluation performed.

One human cadaver study (3 limbs) was also conducted according to the Instruction for Use. The limb studies were utilized to obtain particulate from the atherectomy procedure for a size distribution analysis and to observe device operation in occluded arteries.

2 DEVICE DESCRIPTION AND USE

2.1 Device Description

The FreedomFlow™ Orbital Atherectomy System consists of a Control Module, Tubing Set, and User Handle. It is designed to remove atherosclerotic plaque from peripheral arteries by rotation of diamond-coated spheres mounted eccentrically on a coiled driveshaft. The Control Module is reusable capital equipment. The Tubing Set and User Handle are single-use sterile devices. The User Handle is used to activate rotation and advance the driveshaft on a commercially available 0.014-inch bare-metal atherectomy guidewire. The guidewire and introducer sheath are not included with the system. The Tubing Set and User Handle are the only parts of the system applied to the patient.

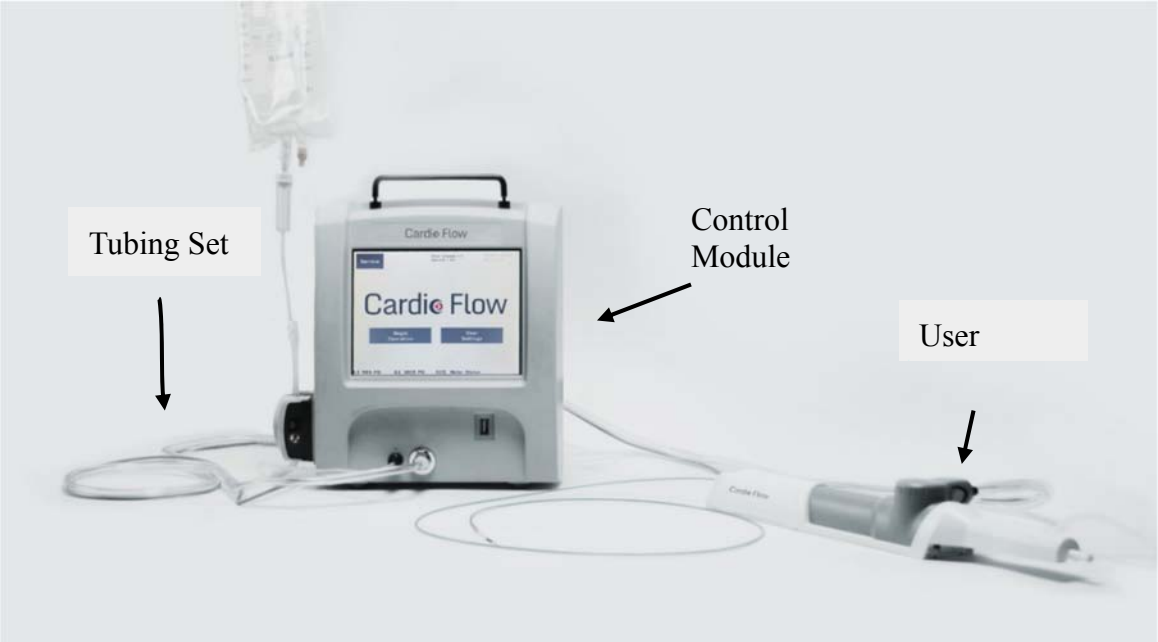

Figure 2-1: FreedomFlow™ Orbital Atherectomy System

2.1.1 Control Module

The Control Module, Model CM1001, is a portable, reusable component of the system that integrates delivery of saline and pneumatic power to the User Handle. The Control Module touchscreen is the primary interface for operating the peristaltic pump and regulating orbital speed of the User Handle. The pre-programmed Control Module includes a pneumatic pressure hose and hospital-grade electrical plug. The Control Module can be placed on a table or mounted to a standard 5-wheel IV pole.

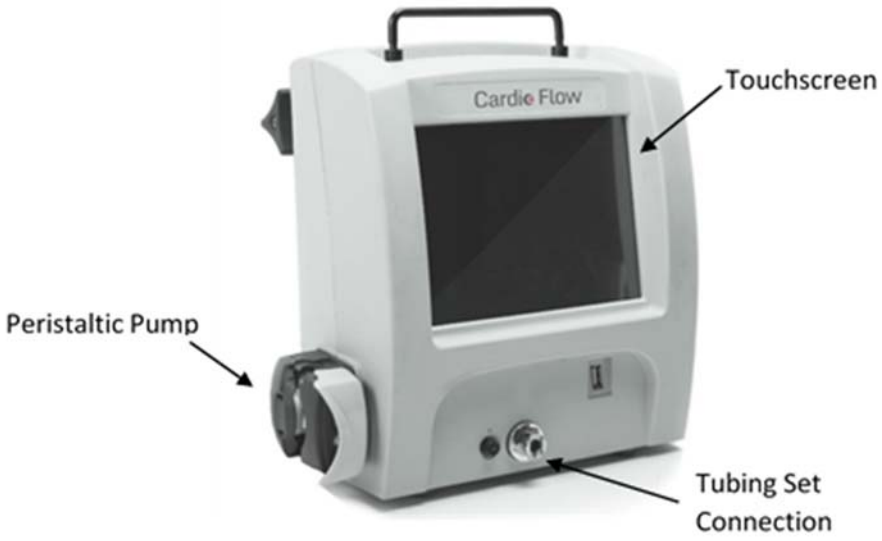

Figure 2-2: Control Module

2.1.2 Tubing Set

The Tubing Set is a single-use component that is packaged with the User Handle. The Tubing Set is supplied sterile (via Ethylene Oxide gas). The set delivers saline and pressurized gas from the Control Module to the User Handle. A cable and sensor relay orbital speed back to the Control Module.

Figure 2-3: Tubing Set

2.1.3 User Handle

The User Handle is a single-use component that provides control over rotation and translational movement of the integrated driveshaft. The User Handle is supplied sterile (via Ethylene Oxide gas). A spring-loaded button on the User Handle is depressed to activate the pneumatic driveshaft and released to stop rotation. The turbine carriage of the User Handle has 7 cm of travel and is used to advance and retract the driveshaft's diamond-coated distal tip and eccentrically mounted diamond-coated spheres independently of the catheter tubing. The User Handle guidewire clamp prevents guidewire movement during use. User Handle H4001 will be evaluated in this clinical trial and can be used to treat a range of vessel sizes. Refer to Instructions for Use for guidance on appropriate vessel sizes that can be treated with User Handle H4001.

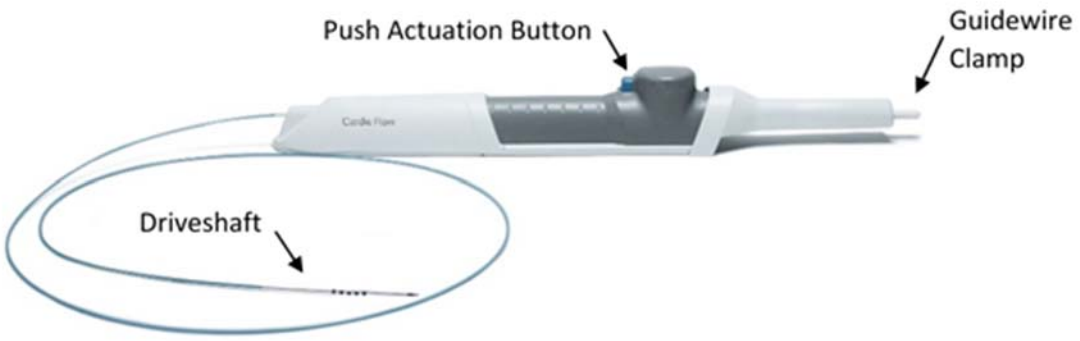

Figure 2-4: User Handle

2.1.4 Driveshaft Details

The driveshaft is a hollow multi-strand cable that drives the spinning of the diamond-coated spheres. The off-axis eccentric attachment of the spheres onto the driveshaft force the spheres in an outward centrifugal direction during rotation. The diamond-coated distal tip is designed to add stability and may ease transition into a tight stenotic lesion.

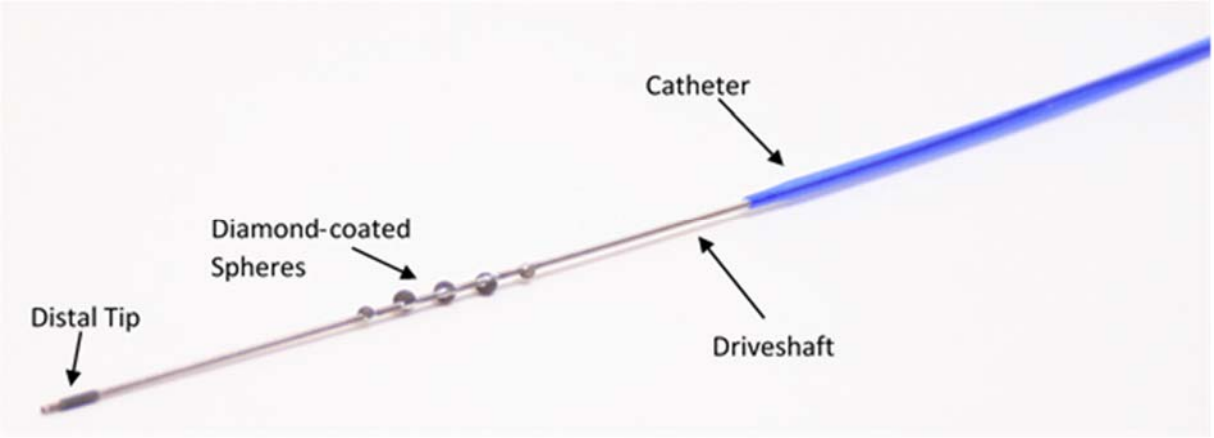

Figure 2-5: Driveshaft Tip

The Cardio Flow Orbital Atherectomy User Handle and Tubing Set are sterile, disposable devices that are intended for use during a single patient procedure and are used with the Control Module, which is a non-sterile, reusable unit that controls system operation.

2.2 Intended Use

The FreedomFlow™ Orbital Atherectomy System is a minimally invasive, catheter-based system designed for improving luminal diameter in patients with PAD.

2.3 Indication For Use

The FreedomFlow™ Orbital Atherectomy System is applied as therapy to remove atherosclerotic plaque within peripheral arterial vessels. The therapy is intended for patients who are acceptable candidates for percutaneous transluminal atherectomy.

3 STUDY PURPOSE AND OBJECTIVE

The primary objective of the study is to evaluate the first-in-human safety and effectiveness of the FreedomFlow™ Orbital Atherectomy System for atherosclerotic plaque removal in *de novo* target lesions in the peripheral vasculature of the lower extremities.

4 STUDY DESIGN

4.1 Overview

This is a first in human (FIH) prospective, two-center, non-randomized single-arm study designed to evaluate the safety and effectiveness of the FreedomFlow™ Orbital Atherectomy System in subjects diagnosed with peripheral arterial disease of the lower extremities.

4.2 Sample Size and Number of Centers

The study may enroll up to 10 subjects and will be conducted at up to 2 investigational sites in the United States.

4.3 Study Duration

Enrollment is expected to take approximately 2 months with observation periods at time of procedure, pre-discharge, 30 days, and 6 months post-procedure follow-up.

5 STUDY ENDPOINTS

5.1 Primary Safety Endpoints

The primary safety endpoint is freedom from a composite of new on-set major adverse events (MAE) through 30-day follow-up as adjudicated by an independent clinical adjudicator.

The components of the MAE are defined as:

- **Cardiovascular related death:** All cardiovascular cause mortality.
- **Myocardial infarction (MI):** Any newly diagnosed MI post procedure, defined as CK-MB ≥2X upper limit normal (ULN).
- **Clinically driven target lesion revascularization (TLR):** any repeat percutaneous or surgical intervention to treat objectively documented symptoms of recurrent ischemia attributable to the treated lesion.
- **Clinically significant target vessel dissection:** NHLBI grade C or greater as confirmed by angiography.
- **Clinically significant target vessel perforation:** NHLBI Type III as confirmed by angiography.
- **Unplanned major target limb amputation:** Amputation of the transmetatarsals or higher that was not previously planned as part of the overall treatment strategy.
- **Clinically relevant distal embolization:** Emboli requiring surgical or medical intervention and/or the presence of symptoms.
- **Pseudoaneurysm:** disruption of the arterial wall at the treatment site as confirmed by angiography.

5.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is technical success. The technical success is defined as the ability of the FreedomFlow™ Orbital Atherectomy System to achieve a residual diameter stenosis ≤50% immediately post treatment without adjunctive balloon inflation, as assessed by an independent Angiographic Core Laboratory.

5.3 Secondary Endpoints

5.3.1 Secondary Safety Endpoints

- Hemoglobin, hematocrit, and free hemoglobin (pre-procedure, immediately post-procedure, and at discharge) will be measured and reported.
- All device and procedure related serious adverse events at 30 days and 6 months post procedure.

5.3.2 Secondary Effectiveness Endpoints

- Clinical Success, defined as the ability of the FreedomFlow™ Orbital Atherectomy System to achieve a final residual diameter stenosis ≤50% with or without adjunctive low pressure balloon therapy, determined by independent angiographic core laboratory.
- Procedure Success, defined as:
  - No procedure-related MAE
  - ≤ 50% residual stenosis at target lesion
  - No device malfunction causing the procedure to be aborted
- Percent of device run time less than 3 minutes cumulative total
- Maximum balloon inflation pressure with adjunctive plain balloon angioplasty and/or drug coated balloon angioplasty
- Improvement of ABIs at 30 days and 6 months
- Improvement of Rutherford Classification at 30 days and 6 months.
- Improvement of patient reported outcomes (PRO, VascuQoL questionnaire) at 30 days and 6 months
- Clinical driven target lesion revascularization (TLR), target vessel revascularization (TVR) at 30 days and 6 months (diagnosis of TLR and TVR to be verified by an angiographic core laboratory)
- Primary patency, primary assisted patency and secondary patency at 30 days and 6 months. Patency will be evaluated by duplex ultrasound and evaluated by a Duplex Ultrasound core laboratory). The restenosis is defined as PSVR of 2.5

6 STUDY PROCEDURE

6.1 Patient Eligibility, Pre-screening and Exclusions

All patients scheduled for a percutaneous endovascular intervention for PAD in the lower extremity will be screened for study eligibility. A Screening/Enrollment Log will be provided to the study sites, in order to maintain a cumulative tracking of all screened patients.

Subjects must meet all inclusion/exclusion criteria for enrollment in the clinical study. Reasons for screening failure(s) will be documented.

6.1.1 Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for participation in the study:

1. Age ≥ 18 years old.
2. Subject is a candidate for percutaneous endovascular intervention for peripheral vascular disease in the lower extremity.
3. Disease is located in the common femoral, superficial femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery.
4. Objective hemodynamic evaluation that subject has a resting ankle-brachial index (ABI) ≤ 0.90, OR subjects with non- compressible arteries (ABI>1.1) must have a toe-brachial index (TBI) of ≤ 0.80.
5. Clinical presentation of lifestyle limiting claudication or rest pain as characterized by Rutherford Classification 2, 3, 4, or 5.
6. Subject has de novo target lesion(s) or lesion(s) treated by percutaneous transluminal angioplasty (PTA) only greater than 3 months prior with stenosis ≥70% by visual estimation in the common femoral, superficial femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery. Up to three lesions can be treated at the index procedure provided the cumulative total lesion length is ≤ 30 cm AND all lesions are in the same leg.
7. Target reference vessel diameter (proximal and distal to target lesion) is 2 to 5 mm by angiographic visual estimation.
8. At least one patent vessel run-off to the ankle or foot at baseline.
9. The target lesion(s) can be successfully crossed with a commercially available 0.014" atherectomy guidewire without any complications during wiring procedure.
10. Subject signs a written Informed Consent form to participate in the study, prior to any study mandated determinations or procedure.

6.1.2 Exclusion Criteria

Subjects must be EXCLUDED from participation in this study if ANY of the following criteria are met:

1. Is female with childbearing potential not taking adequate contraceptives or is currently breastfeeding.
2. Target lesion is within a native graft or synthetic graft.
3. Target lesion is an in-stent restenosis.
4. Chronic total occlusion (CTO) with wire crossed near the advential junction.
5. Subject has significant stenosis or occlusion of inflow tract (upstream

disease) not successfully treated during the index procedure and prior to treatment of the target lesion.

6. History of an endovascular procedure or open vascular surgery on the index limb within 30 days prior to the index procedure.
7. Planned endovascular or surgical procedure within 30 days after the index procedure.
8. Signs and symptoms of systemic infection (temperature of $\geq 38.0°$ Celsius and/or WBC of $\geq$ 12,000 cells/μL) at the time of assessment;
   Note: If infection is adequately treated and controlled (temperature < 38.0° C and WBC < 12,000 cells/μL) patient may be enrolled.
9. Unstable coronary artery disease or other comorbid condition(s) that, in the judgment of the physician precludes safe percutaneous intervention.
10. Significant acute or chronic kidney disease with a creatinine level > 2.5mg/dL and/or requiring dialysis.
11. Evidence or history of intracranial or gastrointestinal bleeding, intracranial aneurysm, myocardial infarction or stoke within 2 months of index procedure.
12. Evidence or history of aneurysmal target vessel.
13. Clinical/angiographic evidence of distal embolization.
14. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.
15. Subjects in whom anti-platelet, anticoagulant, or thrombolytic therapy is contraindicated.
16. Heparin-induced thrombocytopenia (HIT) not able to use Bivalirudin.
17. Uncorrectable bleeding diathesis, platelet dysfunction, thrombocytopenia with platelet count less than 125,000/mm2, known coagulopathy, or INR > 1.5.
18. Thrombolytic therapy within 2 weeks of the index procedure.
19. Intra-operative (intra-procedure) clinical or angiographic complication (other than non-flow limiting dissections) attributed to the use of a currently marketed device prior to introduction of the Cardio Flow atherectomy driveshaft.
20. Has life expectancy < 12 months.
21. Subject is unwilling or unable to comply with the follow-up study requirements.
22. Is currently participating in an investigational drug or device study.
23. Has one or more stents in the treatment vessel.
24. Lacking capacity to provide consent.

6.2 Pre-screening and Written Informed Consent

The site may pre-screen potential subjects by reviewing medical records to identify the study population. Once identified these subjects are approached for the study and consented. The site may not initiate any study specific (non-standard of care) procedures without first obtaining informed consent

Subjects who pass the initial pre-screening will be asked to sign the study specific IRB approved Informed Consent. A member of the research team will approach the subject to obtain informed consent. The background of the proposed study, the procedure, the follow-up schedule and all potential benefits and risks will be carefully explained to the subject prior to obtaining the potential subject's informed consent. A subject is considered "Enrolled" after signing the study specific Informed Consent and if he/she meets all inclusion and exclusion criteria.

Informed consent will be obtained prior to any study specific screening/baseline tests are performed. This does not include any procedures or tests that are obtained via the standard of care related to the subject's non-study related care, prior to undergoing the index procedure.

6.3 Enrollment

Only subjects who meet the inclusion/exclusion criteria, and provide consent will be eligible to receive the treatment and participate in the study. A subject will be considered officially enrolled only if the subject has signed informed consent, meets all the inclusion and none of the exclusion criteria and is treated with the device.

6.4 Baseline Evaluation (Within 30 Days of Index Procedure)

Subjects that meet the pre-screening eligibility criteria and signed informed consent will have the following collected. These evaluations can occur anytime within 30 days of the procedure to the day of treatment. Only one angiogram is required.

- Demographic Information: race, age, weight, height
- Medical History / Current Status
- Physical Exam and Vital Signs
- Angiogram (recorded and sent to sponsor)
- Duplex Ultrasound (if available, recorded and sent to sponsor)
- Rutherford Classification
- Laboratory Assessments:
    - CBC, creatinine, and potassium (on day of procedure)
    - INR & PT if subject is on chronic warfarin therapy (on day of procedure)
    - Urine pregnancy test if female of child-bearing potential (within 7 days of procedure)
    - Hemoglobin, hematocrit, and free hemoglobin (pre-procedure, immediately post-procedure, and at discharge).

- VascuQoL Questionnaire
- Ankle Brachial Index (ABI)
- Concomitant Medications

6.5 Index Procedure

Subjects who meet all of the eligibility criteria will have their scheduled index procedure performed in accordance with physician/investigational site standard practices.

6.5.1 Angiography

At the time of the index procedure, prior to introduction of the Cardio Flow orbital atherectomy device, standard angiography will be performed per the guidelines established by the Angiographic Core Laboratory, to confirm final anatomic eligibility. Subjects who do not meet the final angiographic eligibility criteria, as determined by the investigator at the time of the procedure, will be documented as angiographic screen failures and will not be considered enrolled in the study and no further data will be collected. A subject is considered as "enrolled" after the subject meets all angiographic criteria and a bare-metal atherectomy 0.014" guidewire successfully crosses the target lesion via the true vessel lumen.

Angiography will be performed throughout the procedure to document the treatment outcomes and sent to the sponsor. At a minimum, angiographic images at the following timepoint should be taken.

- Baseline angiography to determine subject's eligibility.
- Post any lesions that are pre-dilated by balloon angioplasty if performed.
- After the Cardio Flow FreedomFlow™ orbital atherectomy treatment session(s).
- Post any adjunctive interventions, e.g. balloon angioplasty and/or stenting, to optimize the outcome or bailout the procedure due to vascular complications.
- Final angiography prior to the end of the procedure.

Up to 3 target lesions are allowed based on the angiographic criteria by this protocol. If 2 or 3 target lesions are selected, the lesion will be numbered based on the anatomic order, i.e. common femoral artery, proximal, middle or distal segment of superficial femoral artery, P1, P2 or P3 segment of popliteal artery, anterior tibial artery, posterior tibial artery, and peroneal artery, regardless of the treatment order.

6.5.2 Non-Target Vessel/Lesion Intervention

Non-target vessels/lesions can be staged and treated with any commercially available devices greater than 30 days prior to or post the index procedure. If a non-target lesion(s) that locates at the iliac artery or at the femoral artery with a vessel size greater than 5 mm in diameter in the target limb and requires intervention during the index procedure, the lesion(s) MUST be treated with commercially available devices prior to the Cardioflow orbital atherectomy procedure. The CardioFlow orbital atherectomy procedure can be performed ONLY if there are no angiographic complications at the non-target vessel/lesion site and downstream vasculatures and no clinical

adverse event. If any angiographic complication at the non-target vessel/lesion site and downstream vasculatures or clinical adverse event occurred, the subject MUST not proceed to the CardioFlow orbital atherectomy procedure. The subject will be considered as an angiographic screening failure.

6.5.3 Cardio Flow FreedomFlow™ Orbital Atherectomy Procedure

Subjects that meet the final angiographic eligibility criteria will have the atherectomy procedure performed according to the Cardio Flow FreedomFlow™ Orbital Atherectomy System Instructions for Use (IFU).

Performing the Atherectomy Procedure

Interventionalist will place commercially available 0.014-inch bare-metal atherectomy guidewire through appropriate size introducer sheath based on User Handle model. See IFU provided with the device for details. If this summary differs from the IFU, follow the IFU

Caution: If the physician suspects the guidewire is placed sub-intimally, the atherectomy procedure must be aborted and alternative care performed.

1. Once the system is prepped with sterile saline, the distal tip of the User Handle driveshaft can be inserted onto the proximal end of the placed guidewire. Ensure that the guidewire clamp at the back of the User Handle is rotated to the open position to allow the guidewire to exit the User Handle.

2. While utilizing imaging technology (fluoroscopy and/or ultrasound), the physician advances the User Handle driveshaft over the guidewire through the introducer sheath and into the patient's vasculature. Continue advancement of the driveshaft and spheres until positioned proximal to the target lesion.

Caution: Verify that the guidewire distal tip is advanced as far distally in patient vasculature as feasible to ensure User Handle driveshaft does not contact the distal tip of the guidewire.

3. Once the driveshaft is in the desired location, rotate guidewire clamp clockwise and verify that the guidewire can no longer freely move. Verify that no saline solution is leaking from the guidewire clamp.

4. Select the appropriate speed for the vessel size on the touch screen.

Caution: A tight lesion stenosis may require a lower speed, prior to sequential higher speed treatments. Start rotation proximal to a tight lesion stenosis.

5. Fully depress the blue activation button to initiate rotation and maintain selected speed.

6. Once rotation is started, slowly advance the turbine carriage forward and backward through the target lesion.

Warning: Performing atherectomy in the presence of severe arterial spasm can result in vessel dissection or perforation. If severe spasm is observed during treatment with the FreedomFlow™ Atherectomy System, immediately stop driveshaft rotation. If no dissections or perforations are detected, resume treatment only after the vessel spasm has spontaneously resolved or is treated pharmacologically. Prophylactic and episodic anti-spasm treatment may be administered as described in section 6.5.4 Procedure Medications in this protocol.

Caution: Do not leave the spheres of the driveshaft in one location for more than 5 seconds during rotation. Smooth, slow, continuous motion of the driveshaft forward and backward is recommended.

Caution: Frequent imaging evaluation, such as contrast fluoroscopy and/or ultrasound, should be utilized throughout the treatment procedure to evaluate lesion removal progress and identify potential dissections. The investigational treatment should be discontinued if a dissection is detected

7. To stop driveshaft rotation, release blue activation button.

Caution: If rotation does not cease with release of blue activation button, disconnect the Tubing Set from the User Handle.

8. To move the driveshaft to a different target lesion, rotate the guidewire clamp counterclockwise to allow the driveshaft to move independently of guidewire.

9. Rotate guidewire clamp clockwise to lock guidewire before activating the driveshaft again.

Removal of the User Handle and Driveshaft

1. Release blue activation button to stop rotation and retract driveshaft proximal to the lesion using the turbine carriage.

2. Rotate guidewire clamp counterclockwise so that User Handle and driveshaft can move independently of guidewire.

3. Carefully remove the driveshaft from the guidewire through introducer sheath.

4. Turn off peristaltic pump by tapping the OFF icon on the Control Module touch screen.

5. Dispose of User Handle and Tubing Set according to standard hospital practice.

Changing a Saline Infusion Bag

To change a saline infusion bag during a procedure, the operation must be paused. If the peristaltic pump door is opened during a procedure, pneumatic power to the User Handle will cease immediately.

1. Remove the User Handle and driveshaft from patient (see instructions above).

2. Turn off peristaltic pump by tapping the OFF icon on the Control Module touch screen.

3. Disconnect current saline infusion bag from IV spike on the Tubing Set and hold the spike upward to prevent the introduction of air.

4. Without touching the sterile IV spike tip, insert a new saline infusion bag onto the IV spike and rehang on the IV pole.

5. Repeat a complete flush cycle of the User Handle and driveshaft.

6.5.4 Procedure Medications

Warning: Performing atherectomy in the presence of severe arterial spasm can result in vessel dissection or perforation. If severe spasm is observed during treatment with the FreedomFlow™ Atherectomy System, immediately stop driveshaft rotation.

Anti-coagulation medication and loading dose of anti-platelet medications will be given prior to the atherectomy procedure per investigational site atherectomy standard procedure. Antispasmodic medications such as nitroglycerine (200 µg intra-arterial (IA) bolus; up to 3000 µg per subject) or papaverine (300 µg IA bolus) may be administered. To avoid frequent IA bolus injections, the following solution (500 ml normal saline with 3000 µg heparin, 3000 µg nitroglycerin and 2.5 mg Cardizem) can be infused intra-arterially at a rate of 6 mL/min. All medications administered for this study should be recorded in the subject's medical record.

During the procedure, any device malfunction and device/procedure related adverse events, including anaphylaxis to medications or device components will be monitored and recorded.

6.6 Post Procedure to Discharge

The following assessments will be performed within 12-24 hours post procedure or prior to hospital discharge, whichever occurs first:

- Physical Exam and Vital Signs
- Hemoglobin, hematocrit, and free hemoglobin
- Adverse Events assessment

6.7 30 Days Follow-up (± 7 Days)

Subjects will return for a follow-up visit at 30 days and the following assessments will be performed:

- Physical Exam and Vital Signs
- Rutherford Classification
- ABI
- Duplex Ultrasound of treated lesion per Ultra Sound Core Lab protocol
- Angiogram – performed only if clinical symptoms requiring intervention during follow-up for TVR or TLR
- VascuQoL Questionnaire
- Adverse Events assessment

6.8 6 Months Follow-up (± 14 Days)

Subjects will return for a follow-up visit at 6 months and the following assessments will be performed:

- Physical Exam and Vital Signs
- Rutherford Classification
- ABI
- Duplex Ultrasound of treated lesion per Ultra Sound Core Lab protocol
- Angiogram – performed only if clinical symptoms requiring intervention during follow-up for TVR or TLR
- VascuQoL Questionnaire
- Adverse Events assessment

Table 6-1: Schedule of Events

Assessment	Screening / Baseline/Pre-procedure	Procedure	Discharge	30 Days (±7 days)	6 months (±14 days)
Informed Consent	X				
Medical History	X				
Physical Exam	X		X	X	X
Laboratory Assessments	X	X			

Urine Pregnancy Test if female	X				
Rutherford Classification	X			X	X
ABI	X			X	X
VascuQoL Questionnaire	X			X	X
Hemoglobin, hematocrit, and free hemoglobin	X	X	X		
Angiogram	X	X		X[a]	X[a]
Duplex Ultrasound	X[b]			X	X
Medications	X		X	X	X
Adverse Events	X	X	X	X	X

[a] Angiograms will be performed at the follow-up visits for verification of restenosis of the treated lesion/vessel site(s) only if the subject has clinical symptoms requiring intervention.

[b] if available

6.9 Unplanned Follow-up

Subjects returning for unscheduled visits complaining of new signs and/or symptoms will be documented as an unplanned follow-up and, at the investigators' discretion perform diagnostic evaluations. The reason should be reported as an adverse event if applicable.

6.10 Subject Early Discontinuation / Withdrawal and Replacement of Subjects

All subjects are informed of their right to withdraw from the clinical study at any time. Additionally, the investigator may prematurely discontinue any subject's participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. However, it is anticipated that such withdrawals will be infrequent to ensure the integrity of the study. The reason for early discontinuation will be documented in the source documents and case report forms.

6.11 Lost to Follow-up

Every attempt will be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information will include three attempts to make contact

via telephone and if unsuccessful, then a certified letter from the investigator will be sent to the subject's last known address.

7 BENEFIT / RISK ANALYSIS

7.1 Benefits

Participation in this study is voluntary. There will be no direct benefits of participating in this study. Information gathered from this study will help confirm the safety and efficacy of the device in treating de novo, severely calcified peripheral lesions.

7.2 Risks

The risks of the investigational procedure to subjects is similar to that of other Atherectomy procedures.

Possible risks associated with the Cardio Flow FreedomFlow™ Orbital Atherectomy System that may occur and/or require intervention include, but are not limited to:

- Allergic reaction to medication/media/device components
- Amputation
- Anemia
- Aneurysm
- Bleeding complications which may require transfusion
- Cerebrovascular accident (CVA)
- Death
- Distal embolization
- Device embolization
- Entry site complications including hematoma
- Hemolysis
- Hypotension/hypertension
- Infection
- Myocardial infarction
- Pain
- Pseudoaneurysm
- Restenosis of treated segment that may require revascularization
- Renal insufficiency/failure
- Slow flow or no reflow phenomenon
- Dissection
- Perforation
- Thrombus

- Vessel closure, abrupt
- Vessel injury, including dissection and perforation that may require surgical repair
- Vessel spasm
- Vessel occlusion

7.3 Minimization of Risk and Monitoring Procedure

Cardio Flow, Inc. has attempted to mitigate risks as much as possible through product design, testing, and through careful labeling and instructions for use.

8 STATISTICS

This study is a one or two center, prospective, non-randomized single-arm Early Feasibility Study. All clinical endpoints will be summarized with descriptive statistics without hypothesis testing. For continuous variables, the range (minimum, maximum), mean, standard deviation, median, first and third quartiles (Q1 and Q3) may be reported, while for discrete variables, count and percentage will be provided.

9 DATA MANAGEMENT

9.1 Subject Identification

Subjects that successfully pass the screening tests and wish to participate in the study will be assigned a unique identification code (ID) using the format "XXX-YYY" where:

XXX = Institution Number, assigned by the Sponsor to each study site

YYY = Enrollment Number, assigned by the institution as each subject is enrolled in the study

In addition to the ID, each subject's initials will be used as an identifier included on documentation submitted to the Sponsor.

9.2 Central Database

All study documentation will be collected and compiled in a central database. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

9.3 Source Documents

Case Report Forms (CRFs) are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, for example. Source documents should be kept in a secure, limited access area. Sponsor may request copies of de-identified source document to adjudicate adverse events.

9.4 Data Collection

Data will be collected on electronic CRFs supplied by the Sponsor or designee. The principal investigator is responsible for the prompt reporting and accuracy and completeness of all study documentation. The study data are entered into the eCRFs. Corrections made after the Investigator's review and approval must be reapproved by the Investigator.

A unique study number will be assigned to each subject. All information recorded on the CRF about the subject will be recorded with the study number on it. The main database will contain only the study number to identify the subject. The code with subject name and study number will be maintained in a secured location.

9.5 Data Processing

Data will be entered / loaded in a validated electronic database using a clinical data management system. Visual and computer error checks will be carried out. The investigator will be queried on errors concerning completeness and consistency. An electronic audit trail system will be maintained with the clinical data management system to track all data changes in the database once the date has been entered/loaded. Regular backups of the electronic data will be performed.

9.6 Study Report

An interim 30-day report summarizing all relevant observations will be prepared following receipt of all patient data forms. A final report will be prepared following study completion.

10 STUDY ADMINISTRATION

10.1 Monitoring

10.1.1 Monitoring Procedures

It is the responsibility of the study sponsor to ensure that proper monitoring of this investigation is conducted. Appropriately trained monitors, appointed by the study sponsor, will complete any monitoring that is done. The monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement

- The Investigational Plan
- Appropriate laws and regulations
- Any conditions of approval imposed by the reviewing IRB and/or other regulatory agencies

The clinical study will be monitored according to the guidelines summarized below. The sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures.

A study specific monitoring plan standardizes monitoring activities across centers to ensure human subject protection and verify data integrity. The monitors shall receive study specific and protocol training prior to conducting any monitoring visits. Study monitors are selected based on their training, qualifications and experience to monitor the progress of an investigation. This study monitoring will include a site qualification, study initiation, interim, and close out visits. All study monitors will be required to follow the study monitoring plan and monitoring standard operating procedures.

The study monitoring will be done by the following Sponsor representative:

Libra Medical Inc

8401 73rd Ave North, Suite 63

Brooklyn Park, MN 55428

10.1.2 Monitoring Visit

The following factors will be taken into account when determining the frequency of the monitoring visits: subject accrual rate at each center, total number of subjects enrolled at each center, and Clinical Investigation Plan compliance at each center. It is anticipated each site will be monitored at least once upon the completion of the 30-day follow-up visits for all enrolled subjects at the study site. Monitors will require direct access to subjects' medical records pertinent to the study (and study inclusion criteria), study management documents, regulatory documents and Subject Informed Consent documents, as well as other potential applicable records not listed here.

Monitors may ensure the clinical investigators have and continue to have staff and facilities to conduct the clinical investigation safely and effectively. Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current IRB-approved informed consent was signed and dated by each subject prior to participating in the study required procedures.

- Verification of documentation in the subject's record that informed consent was signed prior to initiation of the study procedures and that a copy of the signed and dated consent was provided to the subject.
- Source documentation verification by reviewing the CRFs against source documentation for accuracy and completeness of information.
- Verification that the investigation is conducted according to the Clinical Investigation Plan, Instructions for Use and, all malfunctions/ IFU deficiencies are reported as required.
- Verification that subjects met study enrollment criteria.
- Verification that study deviations are documented and reported.
- Verification that the procedures for recording and reporting adverse events to the sponsor are followed.
- Ensuring proper error correction.
- Verification of training documentation of all study personnel participating in study related activities.
- Reviewing all correspondence and regulatory documents, including confirmation of IRB-approved Clinical Investigation Plan or amendments.
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.

Each monitoring visit will be documented via a monitoring report and follow-up letter. The follow-up letter shall be sent to the Investigator to document issues identified, corrective actions and if applicable preventative actions. At subsequent visits any issues resolved shall be documented in this letter to demonstrate resolution.

10.1.3 Study Closure

Study closure is defined as a specific date that is determined by study completion and/or regulatory requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or by decision of the Sponsor or FDA. Study closure visits will be conducted at all enrolling clinical sites in order to review record retention requirements with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit, etc.) Monitoring visits will be conducted by trained monitors and designees. The Monitoring Plan identifies the frequency of monitoring and training requirements of the monitors.

10.2 Device Accountability

Access to investigational devices shall be controlled and used only in the clinical investigation and according to the Protocol. Each site will be responsible for tracking the receipt and disposition of all investigational devices. All unused devices must be returned to the Sponsor at the end of the study.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational device, which shall include:

- The date of receipt
- Identification of each investigational device (serial or lot number)
- The date or dates of use
- Subject identification
- Date of return of unused, expired, or malfunctioning investigational device, if applicable
- The Investigator must explain in writing the reasons for any discrepancy noted in device accountability.

11 DEFINITION OF ADVERSE EVENT(S)

For purposes of this study, an adverse event (AE) is defined as any adverse change (i.e., de novo or pre-existing condition) from the subject's baseline medical condition(s) occurring during the course of the study. Adverse events (AE) are any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device. For the purpose of AE documentation, the start of the course of the study is defined as any time after the treatment has been initiated. All AE's will be recorded in the CRF whether considered procedure-related or not, and will be classified as described in this section.

Pre-existing conditions will not be reported as an AE unless there is an adverse change in that condition. Any AE which resolved and then recurred will be reported as a separate AE.

An AE may be volunteered spontaneously by the subject or discovered as a result of questioning or physical examination by an investigator or study staff.

Elective procedures for a pre-existing condition (that has not worsened) are not considered AEs. Non-cardiovascular abnormal laboratory values will not be considered AEs unless:

1) The PI determines that the value is clinically significant,
2) The abnormal laboratory value required intervention, or
3) The abnormal laboratory value required subject termination from the trial.

All adverse events, regardless of relationship to the device, must be recorded, as applicable, on the case report forms provided. Adverse events that occur during this study should be treated by established standards of care, to protect the life and safety of the subjects.

Adverse events shall be assessed and documented at the time of the procedure and at all study follow-up visits. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

11.1 Serious Adverse Events

An adverse event is considered a Serious Adverse Event (SAE) that:

a) led to death

b) led to a serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient hospitalization or prolongation of existing hospitalization, or

4) a medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to body structure or a body function.

11.2 Device Relationship

Determination whether there is a reasonable possibility that a study product or device caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more likely cause.

11.3 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on the health or safety of a subject, any life-threatening problem or death caused by, or associated with a device, if such effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (e.g., ICF, Study Protocol, Instructions for Use (IFU), publications, etc.), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse effect associated with the investigational device occurs, the investigator shall notify the Sponsor and the IRB/EC as soon as possible.

The Sponsor will investigate the event and notify the FDA and all other participating IRBs and investigators. Should the Sponsor determine that an unanticipated adverse effect presents an unreasonable risk to all participating subjects, the Sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/EC, country regulatory bodies and FDA.

11.4 Adverse Event Reporting

The signs, symptoms and sequelae of an underlying AE should not be reported as separate AEs. All AEs must be recorded on a CRF. All AEs also must be described by (a) duration (start and resolution dates); (b) adjudicated for severity; (c) relationship to the study device; (d) action taken to resolve the event; (e) outcome of the event; and (f) whether or not such event is considered to

be serious. Additional information, such as procedural notes, treatment notes, or a signed clinical summary, may be required as supporting documentation for the reported AE.

Pre-existing medical conditions or symptoms occurring prior to the start of the atherectomy procedure should not be reported as adverse events. In the situation where there is a worsening of a pre-existing medical condition or symptom due to a study related procedure, an adverse event should be reported.

For any adverse event that is ongoing at the time of the initial report, periodic follow-up information is required until the adverse event is resolved or is judged to be chronically stable. The site should submit relevant follow-up information related to the adverse event as soon as it is available.

Depending upon the nature and seriousness of the adverse event, the sponsor or designee may request the Investigator to provide copies of the subject's medical records (such as the subject's laboratory tests and hospital records, Investigator summaries, etc.) to document the adverse event.

The Investigator will report all serious adverse events, including unanticipated adverse device effects, to the IRB according to the IRB requirements. A copy of this IRB communication should be sent to the Sponsor. In case of an unanticipated adverse device effect occurred, the investigator must report to the Sponsor within 10 working days of the site first becoming aware of the event.

Within 10 working days of notification, the Sponsor will report all unanticipated adverse device effects to the appropriate authority, all participating investigators, and all reviewing IRBs. The Sponsor will ensure that safety reporting for the study is conducted in compliance with all pertinent requirements and regulations.

11.5 Adverse Event Assessment

11.5.1 Initial Assessment

The investigator must provide the following information:

- Date of onset
- Nature
- Severity
- Duration / date of resolution
- Outcome
- Relationship to investigational device
- Other relevant information

11.5.2 Assessment of Severity

The Investigator must determine the severity of the adverse event according to the following definitions:

- **Mild** - The adverse event is noticeable to the subject, but does not interfere with routine activity; the symptoms are easily tolerated and transient in nature.
- **Moderate** – The adverse event interferes with routine activity but responds to symptomatic therapy or rest; the symptoms are poorly tolerated and sustained.
- **Severe** – The adverse event significantly limits the subject's ability to perform routine activities despite symptomatic therapy. The adverse event requires medical or surgical treatment or results in hospitalization.
- **Life-Threatening** – The subject is at immediate risk of death.

11.5.3 Device Relatedness

An adverse event is considered device-related when the clinical event has a reasonable time sequence associated with use of the investigational device and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event.

The Investigator must provide an assessment of the adverse event according to the following definitions:

- **Definite** – The adverse event is clearly related to the investigational device: the event has a temporal relationship to the investigational device, follows a known pattern of response, or is otherwise logically related to the investigational device, and no alternative cause is present.
- **Probable (Likely)** – The adverse event is likely related to the investigational device: the event has a temporal relationship to the investigational device, follows a known or suspected pattern of response, or is otherwise logically related to the investigational device, but an alternative cause may be present.
- **Possible (Unlikely)** – The adverse event is unlikely related to the investigational device: the event does not follow a clear temporal relationship to the investigational device or does not follow a known pattern of response, or is otherwise likely to be due to the subject's clinical state or other modes of therapy.
- **Not Related** – The adverse event is clearly not related to the investigational device: the event has no temporal or other relationship to the administration of the investigational device follows no known or suspected pattern of response, and an alternative cause is present.
- **Unknown** – Unable to determine the relationship based on all available information.

11.6 Device Deficiency or Malfunction

A Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate

labeling). Sponsor, in cooperation with the CEC, will assess all device deficiencies that could have led to a serious adverse device effect for potential regulatory reporting requirements.

In the event of a suspected malfunction or device deficiency, the investigational device(s) shall be returned to the manufacture for analysis. Instructions for returning the investigational device will be provided by the Sponsor.

11.7 Reporting of Death

During the study, all deaths must be reported to the Sponsor within the period outlined in Table 12-1. All deaths also should also be reported on the AE form and End of Study CRF. A copy of the subject's death records, medical records for the events that led to the subject's death, and a death certificate (if available) and an autopsy report (if performed) should be sent to the sponsor. In addition, subject death must be reported to the IRB in accordance with IRB requirements.

12 STUDY ADMINISTRATIV OVERSIGHT

12.1 Core laboratory

Independent core laboratories shall be utilized to provide a standardized process and assessment of all angiographic and duplex ultrasound studies. The core laboratories will be responsible for analyzing the angiograms and ultrasound images according to the study eligibility criteria, the study endpoints and this study protocol, for providing feedback to the sites and Sponsor regarding the quality of the tracings and images and for providing a written summary report of all angiograms and duplex ultrasound results to the study Sponsor.

Investigators will enroll subjects into the study based on inclusion and exclusion criteria. Lesion characteristics and measurements will be assessed by investigators using visual estimates; however, the core laboratory will assess by quantitative angiography. Baseline measurements and post-procedure results will be reported by investigator and by core laboratory.

Angiographic and Ultra Sound Core Laboratory Protocols shall be provided to the investigational sites.

12.2 Clinical Adverse Event Adjudication

An Independent Adverse Event Adjudicator will be responsible for the adjudication of any events. For this small-scale feasibility study, one physician independent of the study or the sponsor will be responsible for the adjudication of any events that may be considered serious and/or device related by the principal investigator and/or study Sponsor. The physician will be familiar with PTA procedures who is not an investigator in the trial. The adjudication process will include determination of whether the event or device deficiency constitutes a SAE or an UADE, or contributes to the endpoint, and whether the subject should be considered a Procedural Success. All available data (including lab reports, films, discharge reports, etc.) will be available to adjudicate the events.

12.3 IRB Approval

The study protocol shall be reviewed and approved by the investigator's IRB prior to subject enrollment. The Sponsor must review any proposed changes to the investigational informed consent prior to implementation.

Prior to shipment of investigational devices, a signed copy of the IRB approval letter identifying the clinical study and investigational site is required to be submitted to the Sponsor. Investigators are responsible for obtaining and maintaining annual renewal of the study by their IRB (or according to renewal schedule imposed by the IRB). Evidence of renewal and continued IRB approval must be provided to the Sponsor accordingly.

12.4 Informed Consent

Informed consent is mandatory and must be obtained from all subjects per local regulations, prior to their participation in the study. Only IRB approved informed consent may be used.

It is the responsibility of the Investigator to ensure written informed consent from each subject, or the legally authorized representative of the subject, is obtained prior to the initiation of any study-related procedures.

Subjects who agree to participate in this study will do so voluntarily. They will be treated on an equal basis with all other patients. Choosing not to participate will not affect their care in any way.

Study personnel fully knowledgeable in the purposes and procedures of the study will approach all prospective study participants. The facilities and settings in which prospective participants will be presented with the opportunity to learn about and consent to participation in the study will provide them sufficient quiet and unhurried time to be informed of the study, to ask questions, and between consent being given and the initiation of study procedures. Study personnel will, after presenting the study to prospective participants, assess the subject's understanding and autonomy by asking the subject to explain the study in his/her own words.

Once that step is completed, consent will be able to be given by the subject's signing the consent form. A copy of the consent form will be given to all consented participants.

Original signed subject consent forms must be retained in the study files by the Investigator, and available for review by the Sponsor and/or regulatory agencies, as applicable.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available, or if there is an amendment to the protocol which necessitates a change to the content of subject information and/or to the consent form. The Investigator will inform the subject of changes in a timely manner, and will ask the subject/patient to confirm his/her continuation in the study by signing a revised consent form.

Any revised informed consent form and other written information provided to subjects must receive IRB, Sponsor, and regulatory agency approval, as applicable.

12.5 Records

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the study investigation. The final responsibility for maintaining such records remains with the Investigator. These records include, but not limited to:

- All signed agreements;
- IRB/EC approval letter(s);
- Signed ICF;
- Records of AEs, including supporting documents;
- Records of protocol deviations, including supporting documents
- Records showing receipt, use and disposition of all investigational devices, including:
    - Date, quantity, model and serial numbers of devices received,
    - Name of person(s) who received, used or disposed of each device,
    - The number of devices returned to the Sponsor and the reason(s) for return;
- All correspondence related to the study;
- Records of each subject's case history, including study-required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, etc.;
- Study personnel visit log;
- Signature authorization and delegation log; and,
- Any other records that applicable regulation requires to be maintained.

The Investigator will maintain all essential trial documents and source documentation that support the data collected on the study subjects in compliance with FDA's GCP guidelines. Documents must be retained until at least 2 years have elapsed since the date the investigation is completed or terminated or the records are no longer required to support a regulatory submission, whichever date is later. These documents will be retained for a longer period of time by agreement with Sponsor or in compliance with other regulatory requirements. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. The Sponsor must receive written notification of this custodial change.

12.6 Reports

Table 12-1 lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the EC/IRB reporting requirements for their respective site. If applicable regulations or EC/IRB requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 12-1: Reports Required from Investigators to Sponsor

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, EC/IRB	As soon as possible but within 5 working days of knowledge
Death	Sponsor, EC/IRB	Written reports (e.g., via e-mail) within 48 hours
SAE	Sponsor EC/IRB, if required	Within 10 working days of knowledge Per IRB requirement
Device malfunction with clinical sequelae	Sponsor EC/IRB, if required	Within 48 hours via written communication. Return the device to sponsor within 48 hours.
Serious protocol deviations (e.g., ICF not obtained, to protect the life or physical well-being of a subject in an emergency)	Sponsor, EC/IRB	As soon as possible but within 5 working days of knowledge Per IRB requirement
Withdrawal of EC/IRB approval	Sponsor	Within 5 working days of knowledge
Annual progress report	Sponsor, EC/IRB	Annually
Interim report	Sponsor, EC/IRB	Within 14 days of 30-day follow up
Final report	Sponsor, EC/IRB	Within 3 months of study completion or termination
Note: Each IRB/EC may require more stringent reporting requirements that those listed in this table.		

12.7 Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement.
- Obtain approval from the IRB including subsequent protocol amendments and changes to the Informed Consent form and obtaining annual IRB approval and renewal throughout the duration of the study.
- Await IRB approval, as well as, any additional hospital requirements prior to

requesting written informed consent from any potential study subject or prior to allowing any subject to participate in the study.

- Complete and provide signed copies of all required investigator documentation such as an Investigator Agreement or Disclosure of Financial Interest.
- Agree to participate in Investigator meetings as scheduled by the Sponsor.
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol.
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions).
- Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP.
- Be willing to change hospital routine if required by protocol (as long as subject safety and well-being is not compromised).
- Control any investigational device(s) stored at their site.
- Be aware of, and comply with, GCP and applicable regulatory requirements.
- Permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authorities.
- Have available an adequate number of qualified staff and adequate facilities to properly conduct the study.
- Ensure study personnel are adequately informed about the protocol, the investigational device and study-related duties and functions.

12.8 Sponsor Responsibilities

The Sponsors responsibilities in the study include:

- Selecting the Principal Investigator(s), all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.
- Provide study protocol, device, and GCP training to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Select all qualified clinical Investigators and study sites and other consultants (e.g., the study monitors) who participate in the study.
- Provide financial support to each study site.
- Follow/promote all regulatory standards per appropriate regulations for study sites, core laboratories, and other participants, and ensure compliance by periodically monitoring sites.
- Ensure completion of site monitoring of clinical data at each clinical study site.

- Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes only.
- Review and approve publication of study results in the literature

12.9 Protocol Deviations / Violations and Medical Emergencies

A protocol deviation or violation is a failure to comply with the requirements of the clinical study as specified in the protocol. Examples of protocol deviations include late visits, missed visits, required follow-up testing not completed. An example of a major protocol violation includes enrollment of a study subject who fails to meet inclusion/exclusion criteria as specified in the protocol. Each investigator shall conduct this clinical study in accordance with the study protocol and any conditions required by the reviewing IRB.

Deviations/violations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place. See Table 12-1: Reports Required from Investigators to Sponsor for reporting timelines for emergency deviation.

12.10 Pre-Study Documentation Requirements

Prior to shipment or receipt of investigational product, the following documents must be provided to Cardio Flow, Inc.:

- Signed protocol/protocol amendments
- Signed and dated Investigator Agreement(s)
- A copy of the written IRB approval of the protocol
- A copy of the written IRB approval of the Informed Consent Form
- Signed and dated Curriculum Vitae of the Investigator(s)
- Copy of the Investigator(s)' current medical license(s), or equivalent
- Signed and dated Non-disclosure Agreement(s), if required
- Signed and dated Certification/Financial Disclosure Form(s)

12.11 Criteria for Terminating Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators and associated IRB will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue development of the device.

12.12 Publication Policy

It is anticipated that the investigators involved may publish the results of this study. It is expected that the results will initially be written in abstract form and submitted to a meeting such as TCT or ACC and then submitted to a peer reviewed medical journal.

13 REVISION HISTORY

Date	Description
May 1, 2017	Version 1.0. Initial Release
May 31, 2017	Version 2.0. Clarify that H4001 device will be used in this trial.
June 28, 2017	Version 3.0. Clarify how target lesions will be numbered.
July 7, 2017	Version 4.0. Incorporate PI's comments
October 4, 2017	Version 5.0. Incorporate FDA's comments from IDE G170219 disapproval letter dated September 29, 2017
November 18, 2017	Version 6.0 Incorporates FDA's email request to insert warnings about the possibility of vasospasm and potential tissue damage and preventive measures. Added Exclusion of subjects Lacking capacity to provide consent.

14 BIBLIOGRAPHY

1. Mohler ER. Peripheral arterial disease: identification and implications. Arch. Intern. Med 2003;163: 2306-2314.
2. Hirsch AT, Haskal ZJ, Hertzet NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). Accessed Apr 27, 2007. Available at URL address: http://www.acc.org/clinical/guidelines/pad/index.pdf.
3. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287(9):2570-2581.
4. Bashir R, Cooper CJ. Evaluation and treatment of peripheral arterial disease. Curr Opin Cardiol. 2003;18(6):436-443
5. Brunton S, Belotserkovaya Y, Marinovich A, Mirohnik M, Monahemi P. A practical look at the long-term management of intermittent claudication. Resident & Staff Physician. 2003; 49(9):10-15.
6. Criqui MH. Peripheral arterial disease—epidemiological aspects. Vasc Med. 2001; 6(suppl 1):3-7.
7. Comerota AJ. Endovascular and surgical revascularization for patients with intermittent claudication. AmJ Cardiol. 2001;87(suppl):34D-43D.
8. Dermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, Sharma L, Clark E, Gibson D, Martin GJ. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA. 2001;286(13):1599-1606.
9. Criqui MH, Fronek A, Barrett-Connor E et al. The prevalence of peripheral arterial disease in a defined population. Circulation 1985a; 71: 510-15.
10. Murabito JM, D'Agostino RB, Silbershatz H, et al. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation 1997;96:44-9.
11. Bainton D, Sweetnam P, Baker I, et al. Peripheral vascular disease: consequence for survival and association with risk factors in the Speedwell prospective heart disease study. Br Heart J 1994; 72:128-32.
12. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. N Engl J Med 2002;347:1941- 51.
13. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark E. The ankle-brachial index is associated with leg function and physical activity: the walking and leg circulation study. Ann Intern Med 2002;136(12):873-83.
14. Hirsch AT, Ekers MA. A comprehensive vascular medical therapeutic approach to peripheral arterial disease: the foundation of effective vascular rehabilitation. In: Fahey VA, ed. Vascular Nursing. 3rd ed. Philadelphia, Pa: WB Saunders; 1999:188-211.
15. Jamsen T, Manninen H, Tulla H, et al. The final outcome of primary infrainguinal percutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. J Vasc Interv Radiol 2002;13:455- 63.
16. Vroegindeweij D, Tielbeek AV, Buth J, et al. Directional atherectomy versus balloon angioplasty in segmental femoropopliteal artery disease: two-year follow-up with color-flow duplex scanning. J Vasc Surg 1995;21:255- 68; discussion 268-9.
17. Laird Jr J. R., Reiser C., Biamino G., Zeller T. Limb Salvage for Chronic Arterial Occlusive Disease: Indications And Management. J Cardiovasc Surg (Torino) 2004 :45(3), 239 – 248.
18. Isner JM, Pieczek A, Schainfeld R, et al. Clinical evidence of angiogenesis after arterial gene transfer

of phVEGF165 in patient with ischaemic limb. Lancet 1996;348:370-4.

19. Ingle H, Nasim A, Bolia A, et al. Subintimal angioplasty of isolated infragenicular vessels in lower limb ischemia: long-term results. J Endovasc Ther 2002;9:411-6. Erratum in: J Endovasc Ther 2002;9:A-6.

20. Jacobs D, Motaganahalli R, Cox D, Wittgen C, Peterson G. True lumen re-entry devices facilitate subintimal angioplasty and stenting of total chronic occlusions: Initial report. Journal of Vascular

21. Surgery, 2006:43(6), 1291-1296.

22. Piotrowski JJ, Pearce WH, Jones DN, Whitehill T, Bell R, Patt A, Rutherford RB. Aortobifemoral bypass: the operation of choice for unilateral iliac occlusion? J Vasc Surg. 1989 Jul;10(1):105-6.

23. Powell RJ, Fillinger M, Walsh DB, et al. Predicting outcome of angioplasty and selective stenting of multisegment iliac artery occlusive disease. J Vasc Surg 2000;32:564-9.