Evaluation of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System to Treat Peripheral Artery Disease

(FAST II Trial)

Protocol Number:	010-055
Version	F
Date	April 2, 2020
Investigational Products	• Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System - Pneumatic • Cardio Flow Freedom Flow™ Orbital Circumferential Atherectomy System - Electric
Regulatory Status	Limited to Investigational Use Only
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Vascular Ultrasound Core Laboratory	Massachusetts General Hospital The Vascular Ultrasound Core Laboratory (VASCOR) 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: **Evaluation of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System to Treat Peripheral Artery Disease (FAST II Trial)**

PROTOCOL NUMBER: 010-055

PROTOCOL VERSION: F

PROTOCOL DATE: April 2, 2020

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	010-055, Version F
Protocol Title	Evaluation of the Cardio Flow **F**reedomFlow™ Orbital Circumferential **A**therectomy **S**ystem to **T**reat Peripheral Artery Disease (FAST II Trial)
Investigational Product	Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System - Pneumatic • CM1001 – Control Module • H3001 – 6F User Handle + Tubing Set • H4001 – 5F User Handle + Tubing Set Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System - Electric H6002 – 6F User Handle • H6001 – 5F User Handle • H7001 Power Supply and Mounting Bracket
Study Objective:	To evaluate the safety and effectiveness of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System for atherosclerotic plaque removal and vessel compliance modification in *de novo* native target lesions in the peripheral vasculature of the lower extremities.
Study Design:	Prospective, multi-center, non-randomized single-arm study
Sample Size and Number of Sites:	The study plans to enroll 112 subjects at up to 15 sites in the United States with approximately 56 patients using the Pneumatic System and approximately 56 patients using the Electric System .
Primary Safety and Effectiveness Endpoints:	Primary effectiveness endpoint is technical Success defined as the ability of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System to achieve a residual diameter stenosis ≤50% without adjunctive therapy, as assessed by an independent Angiographic Core Laboratory. Primary safety endpoint is freedom from a composite of new onset major adverse events (MAE) at 30-day follow-up as adjudicated by an Independent Clinical Events Committee. The components of the MAE are defined as: 1. **Cardiovascular related death:** All cardiovascular cause mortality. 2. **Myocardial infarction (MI):** Any newly diagnosed MI post procedure, defined as CK-MB ≥2X upper limit normal (ULN). 3. **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. 4. **Clinically significant target vessel dissection:** NHLBI grade C or greater as confirmed by angiography. 5. **Clinically significant target vessel perforation:** NHLBI Type III as confirmed by angiography. 6. **Unplanned major target limb amputation:** Amputation of the transmetatarsals or higher that was not previously planned as part of the overall treatment strategy. 7. **Clinically relevant distal embolization:** Emboli requiring surgical or medical intervention and/or the presence of symptoms. 8. **Pseudoaneurysm:** Disruption/weakening of the arterial wall at the treatment

	site as confirmed by angiography.
Secondary Endpoints:	1. Clinical Success, defined as ≤50% residual stenosis at target lesion with or without adjunctive therapy, as assessed by an independent Angiographic Core Laboratory. 2. Procedure Success, defined as ≤50% residual stenosis at target lesion with or without adjunctive therapy, no procedure-related MAE, no device malfunction causing the procedure to be aborted 3. Improvement of ABI at 30 days and 6 months 4. Improvement of Rutherford Classification at 30 days and 6 months 5. Improvement of patient reported outcomes (PRO, VascuQoL questionnaire) at 30 days and 6 months 6. Clinically driven target lesion revascularization (TLR) at 6 months, target vessel revascularization (TVR) at 30 days and 6 months (as assessed by an independent Angiographic Core Laboratory) 7. 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 an independent Vascular Ultrasound Core Laboratory). The restenosis is defined as peak systolic velocity ratio (PSVR) of 2.5.
Statistical Considerations	The study is designed as a prospective, multi-center, nonrandomized single arm study and powered for the primary safety endpoint of freedom from MAE at 30 days and primary effectiveness endpoint of technical success. The sample size is calculated to simultaneously power for the primary effectiveness and primary safety endpoints by comparing to the pre-specified Performance Goal (PG). Primary Safety Endpoint Literature review through a random effect meta-analysis showed a 95% freedom from MAE at 30 days. The pre-specified performance goal for the primary safety endpoint is 85% based on an allowed 10% margin. The hypotheses are H_0: Freedom from MAE at 30 days $\leqslant$ 85% vs. Ha: Freedom from MAE at 30 days > 85%. Under an exact, one-sided test for a single binomial proportion at the 0.025 significance level, a sample size of 102 mITT subjects will be required to provide at least 90% power to meet this primary safety objective. Primary Effectiveness Endpoint Sample size estimates were calculated for the primary effectiveness outcome by comparing the technical success rate to the pre-specified performance goal of 86% (i.e., H_0: technical success rate $\leqslant$ 86% vs. Ha: technical success rate > 86%). The performance goal of 86% was derived using a random effect meta-analysis based on the technical success rates that were obtained from the results of recent atherectomy studies and the allowed 10% margin. The underlying technical success rate was assumed 96%. Under an exact, one-sided test for a single binomial proportion, at the 0.025 significance level, a sample size of 101 mITT subjects will be required to provide 90% power to meet this technical success objective. Overall Sample Size In order to adequately power for both primary effectiveness and primary safety hypotheses, we require a sample size of 102 mITT subjects who complete 30 days

	follow-up. The dropout rate of mITT subjects is assumed to be 10 %. The final sample size for the study will be 112 subjects. Analysis of Primary Safety and Effectiveness Endpoints The analysis of primary safety and effectiveness endpoints will be performed in the mITT analysis set. The primary safety will be assessed by calculating the proportion of subjects who have no MAE at 30 days aggregated over the mITT subjects. A 95% two-sided confidence interval will be estimated using the Clopper-Pearson interval (F-distribution method). If the lower bound of this 95% confidence interval is greater than the performance goal 85%, we can conclude the primary safety objective is met. Similarly, the primary effectiveness will be assessed by calculating the proportion of subjects who have achieved technical success over the mITT subjects. A 95% two-sided confidence interval will be estimated using the Clopper-Pearson interval (F-distribution method). If the lower bound of this 95% confidence interval is greater than the performance goal 86%, we can conclude the primary effectiveness objective is met. The study will be considered a success if both primary effectiveness and safety objectives are met using the mITT Set at the one-sided 0.025 level of significance in the final analysis. The secondary endpoints will be analyzed with descriptive statistics; there will be no formal statistical hypothesis test. Details of the statistical analyses will be provided in a separate standalone Statistical Analysis Plan.

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. Objective hemodynamic criteria that subject has a resting ankle-brachial index (ABI) ≤ 0.90 **OR** a resting toe-brachial index (TBI) of ≤ 0.80 **OR** ankle pressure of ≤70 mmHg. 4. Clinical presentation of lifestyle limiting claudication, rest pain and/or ischemic wounds as characterized by Rutherford Classification 2, 3, 4, or 5. 5. Disease is located in the common femoral, superficial femoral, popliteal, tibioperoneal, anterior tibial, posterior tibial, and/or peroneal arteries. a) De novo target lesion(s) with stenosis ≥70% by visual estimation **and/or** b) Lesion(s) treated by percutaneous transluminal angioplasty (PTA) and/or atherectomy ≥3 months prior with a restenosis ≥70% by visual estimation. c) Up to three lesions can be treated at the index procedure provided the cumulative total lesion length is ≤ 20 cm AND all lesions are in the same target leg. 6. Target reference vessel diameter (proximal to and distal to target lesion) is 2 to 8 mm by angiographic visual estimation. 7. At least one patent vessel run-off to the ankle or foot at baseline. 8. The target lesion(s) can be successfully crossed with a commercially available 0.014" atherectomy guidewire without any complications during wiring procedure. 9. 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:* *Exclusion Criteria* 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. Target lesion is a chronic total occlusion (CTO) with occlusion length greater than 10 cm and/or with wire crossed sub-intimally. CTO wire placement in true lumen must be confirmed via IVUS prior to enrollment. 5. Subject has significant stenosis or occlusion of inflow tract (upstream disease) not successfully treated during the index procedure or prior to treatment of the target lesion. 6. 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. 7. Evidence or history of aneurysmal target vessel.

	8. Clinical/angiographic evidence of distal embolization prior to intervention. 9. History of an endovascular procedure or open vascular surgery on the index limb within 30 days prior to the index procedure (other than treatment of inflow tract disease). Endovascular procedure or open vascular surgery on the non-index limb cannot be staged within 2 weeks prior to the index procedure. 10. Planned endovascular or surgical procedure prior to the subject's 30 day follow up. 11. Signs and symptoms of systemic infection (temperature of ≥ 38.0° Celsius and WBC of ≥ 12,000 cells/μL) at the time of assessment; Note: If infection is adequately treated and controlled patient may be enrolled. 12. Unstable coronary artery disease or other comorbid condition(s) that, in the judgment of the physician precludes safe percutaneous intervention. 13. Significant acute or chronic kidney disease with a creatinine level > 2.5mg/dL and/or requiring dialysis. 14. Evidence of intracranial or gastrointestinal bleeding, intracranial aneurysm, myocardial infarction or stoke within 2 months of index procedure. 15. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 16. Subjects in whom anti-platelet, anticoagulant, or thrombolytic therapy is contraindicated. 17. Heparin-induced thrombocytopenia (HIT) not able to use Bivalirudin. 18. Uncorrectable bleeding diathesis, platelet dysfunction, thrombocytopenia with platelet count less than 125,000/mm2, known coagulopathy, or INR > 1.8. 19. Evidence of thrombus within target lesion or thrombolytic therapy within 2 weeks of the index procedure. 20. Has life expectancy < 12 months in the opinion of the investigator. 21. Subject is unwilling or unable to comply with the follow-up study requirements. 22. Subject is currently participating in an investigational drug or another investigational device exemption (IDE) study.
Study Duration and Follow-up Period:	Approximately 6 months enrollment period with observation periods at time of procedure, 30 days post procedure and 6 months post procedure. 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 a modified intent-to-treat (mITT) 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 arterial disease of the lower extremities and a strong surrogate marker for atherosclerosis in the vessels of the heart, kidneys, and brain.[1,2,3,4] PAD is associated with a 60% incidence of coronary or cerebrovascular disease.[5] About 90% of patients with symptomatic PAD have coronary artery disease (CAD) as well.[6] The disease can have devastating effects on quality of life and survival, with mortality around 30% at 5 years, 50% at 10 years and 75% at 15 years.[7] Overall, CVD causes death in 75% of PAD patients.

Most common among elderly people, diabetics, and smokers,[8] PAD afflicts an estimated 8-12 million people in the United States alone.[9] 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.[10] 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.[10]

Classic IC only occurs in about 10% of patients with PAD and approximately 40% of the PAD patients do not have leg pain. The remaining half of the PAD patients have a variety of leg symptoms different from classic IC.[8] Even asymptomatic PAD patients, those without IC, have poor physical function.[11] 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.[12] 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.[13] Patients with normal ABIs and IC are advised to undergo an exercise ABI assessment.[4] 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.[14,15]

The overall goals of PAD treatment are to maintain or improve function, reduce or eliminate ischemic symptoms and prevent disease progression.[10] 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).[16] Invasive treatments include bypass surgery, percutaneous transluminal angioplasty (PTA),[17] percutaneous atherectomy (directional or rotational) with or without

balloon angioplasty,[18] endarterectomy, excimer laser combined with PTA[19] and stenting (bare metal and 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,[20] and subintimal angioplasty, in which a new lumen is tunneled between the intima and the media, are under study.[21,22]

Technical challenges involved in treating PAD surgically or percutaneously arise from anatomy, co-existing diseases such as diabetes, restenosis, inflammation and disease progression. Surgery[23] or percutaneous interventions[24] 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 or modifying 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 Circumferential Atherectomy System.

The Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System is intended to remove or modify fibrous and calcified stenotic plaque using diamond-coated eccentric spheres attached to a driveshaft in a spiral configuration. The device is intended to operate over a commercially available 0.014' atherectomy guidewire to treat vessels from 2 mm to 8 mm in diameter. No driveshaft lubricant is required for use with the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System. Two Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System versions are available, each with 6Fr and 5Fr variants: a pneumatic version and an electric version, both of which have the same driveshaft and abrasive element configurations.

A feasibility clinical trial was conducted under IDE G170219 to evaluate the first-in-human (FIH) safety and effectiveness of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System - Pneumatic for atherosclerotic plaque removal in de novo native target lesions in the peripheral vasculature of the lower extremities. The trial was a prospective, 2-center, non-randomized single arm study. The primary safety endpoint was freedom from major adverse events (MAE) at 30 days, and the primary effectiveness endpoint was technical success. The investigational atherectomy device was User Handle H4001 (5Fr) in this trial. A total of 10 patients were enrolled at 2 US investigational sites. There were no protocol defined MAEs in any of the 10 patients through 30 days. Results of the feasibility clinical trial demonstrated that the FreedomFlow™ Orbital Circumferential Atherectomy System - Pneumatic can be safely used in patients with Rutherford Classification 2 to 5 symptomatic femoro-popliteal stenotic or occlusive disease and support the initiation of a pivotal study to further evaluate the safety and effectiveness of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System – Pneumatic, and the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System – Electric, in a larger patient population.

2 DEVICE DESCRIPTIONS AND USE

2.1 PNEUMATIC SYSTEM DESCRIPTION

The FreedomFlow™ Orbital Circumferential Atherectomy System - Pneumatic 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 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.

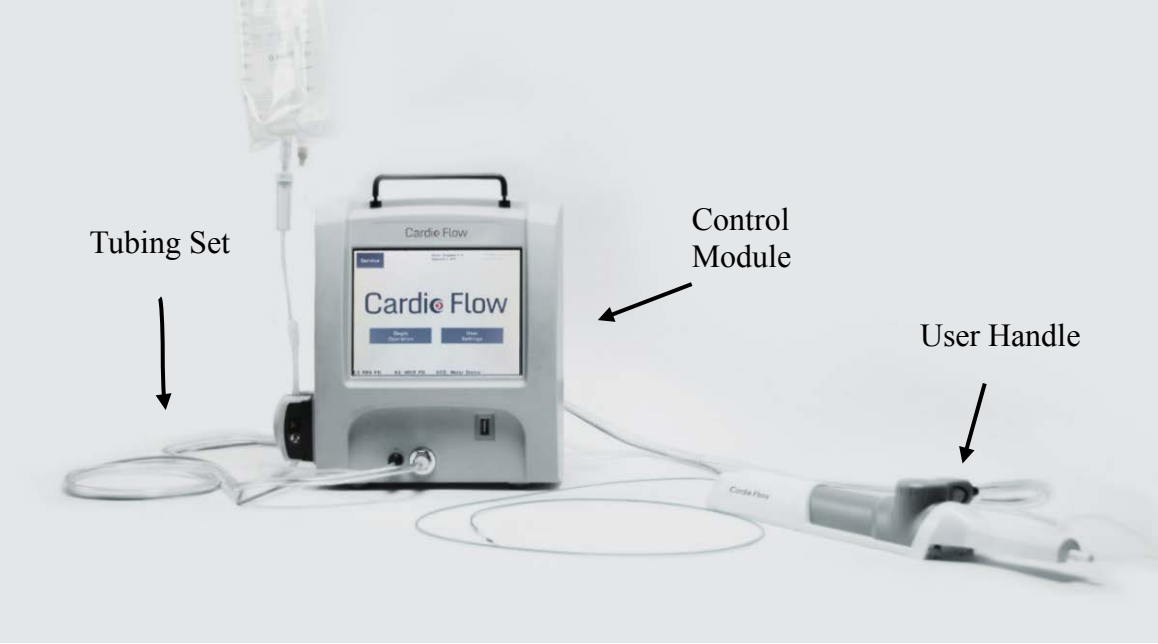


Figure 2-1: FreedomFlow™ Orbital Circumferential Atherectomy System - Pneumatic

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.

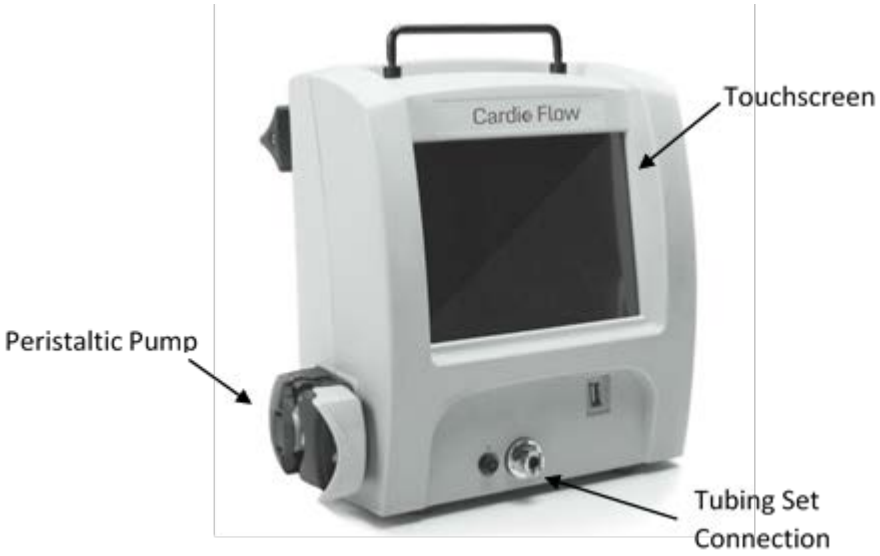


Figure 2-2: Control Module

2.1.2 Tubing Set

The Tubing Set is a single-use component that is packaged with the Pneumatic 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 Pneumatic User Handle

The pneumatic 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. There are two sizes of pneumatic User Handles (H3001 6Fr and H4001 5Fr). Both pneumatic User Handles will be evaluated in this clinical trial and can be used to treat a range of vessel sizes (2mm to 8mm). Refer to 8005 Cardio Flow Instructions for Use for guidance on appropriate vessel sizes.

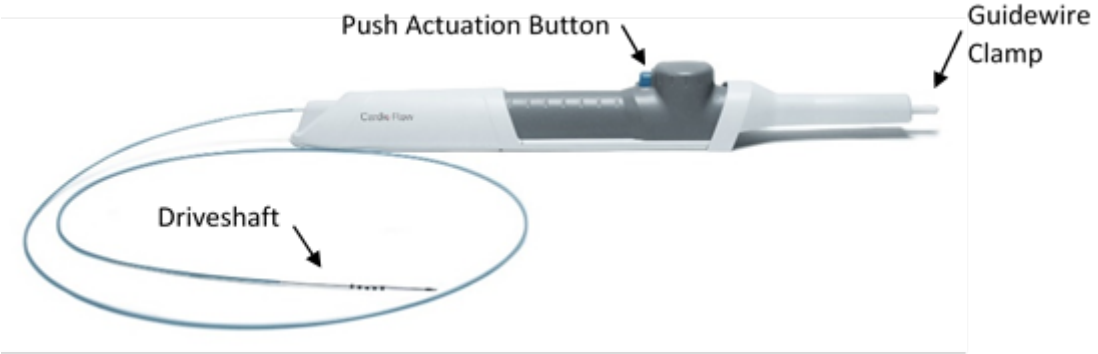


Figure 2-4: Pneumatic User Handle

2.2 ELECTRIC SYSTEM DESCRIPTION

The FreedomFlow™ Orbital Circumferential Atherectomy System, Electric is a flexible over-the-wire rotary driveshaft used to ablate atherosclerotic plaque from arterial blood vessels within the body. The driveshaft is used together with a compatible introducer sheath and 0.014-inch diameter x 300 cm (minimum length) atherectomy guidewire. The driveshaft is introduced into the patient's vasculature by traditional minimally invasive techniques. See Specifications in the 8014 CardioFlow Instruction for Use for information on selecting the appropriate size introducer sheath.

There are two sizes of electric User Handles (H6002 6Fr and H6001 5Fr). Both User Handles will be evaluated in this clinical trial and can be used to treat a range of vessel sizes (2mm to 8mm). Refer to 8014 Cardio Flow Instructions for Use for guidance on appropriate vessel sizes.

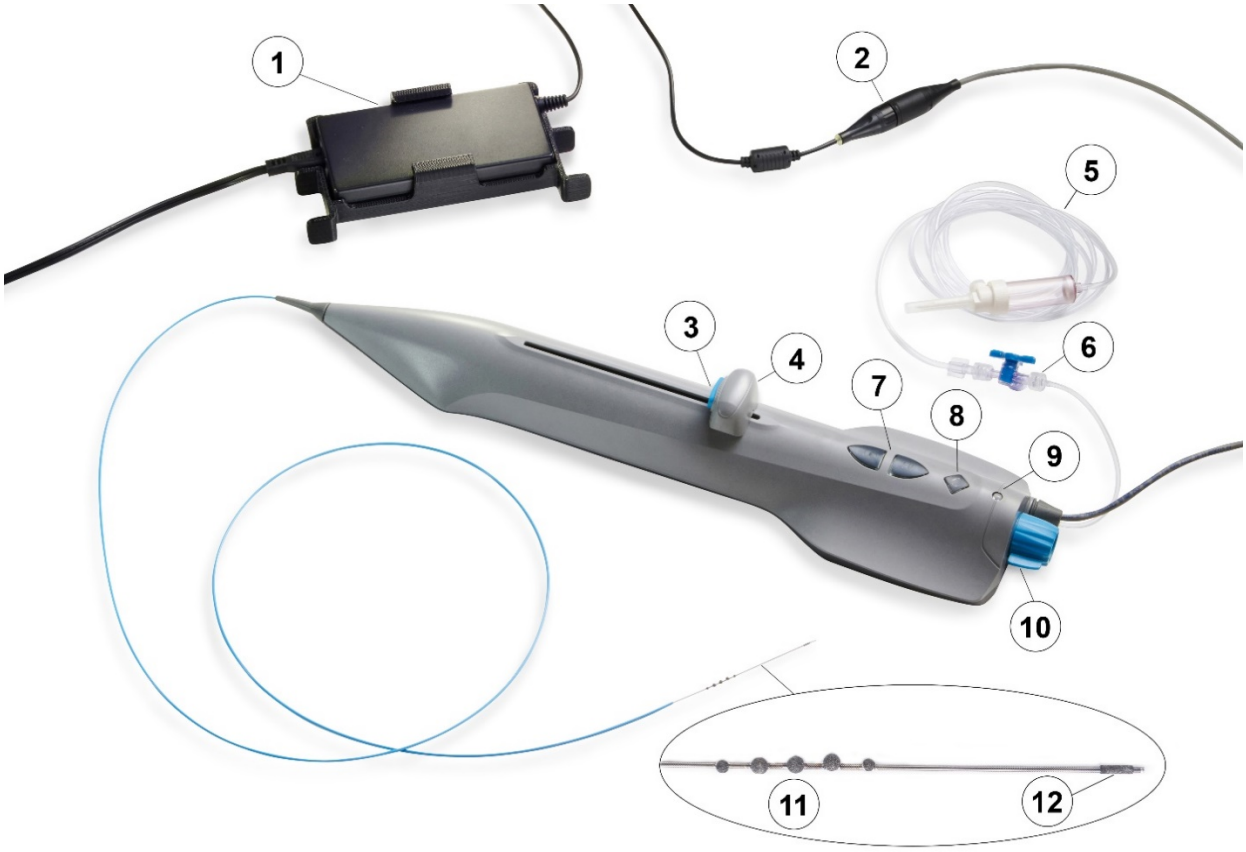
The FreedomFlow™ Orbital Circumferential Atherectomy System - Electric is powered by the Cardio Flow Power Supply H7001, which is a hospital-grade portable, reusable component. H7001 provides DC power to rotate the FreedomFlow™ driveshaft. H7001 also provides DC

power to a saline pump integrated into the electric User Handle. During operation the saline pump delivers saline to the distal tip of the driveshaft.

FreedomFlow™ Orbital Circumferential Atherectomy System - Electric is designed to remove atherosclerotic plaque from peripheral arteries by rotation of diamond-coated spheres mounted eccentrically on a coiled driveshaft. The electric User Handle is used to activate rotation and advance the driveshaft on a commercially available 0.014-inch atherectomy guidewire. The guidewire and introducer sheath are not included with the system. The electric User Handle is the only part of the system applied to the patient.

2.2.1 Electric User Handle

The electric 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 button on the User Handle is depressed to activate the driveshaft and released to stop rotation. The carriage of the User Handle has 12 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. There are two sizes of electric User Handles (H6002 6Fr and H6001 5Fr). Both electric User Handles will be evaluated in this clinical trial and can be used to treat a range of vessel sizes (2mm to 8mm). Refer to 8014 Cardio Flow Instructions for Use for guidance on appropriate vessel sizes.



1. H7001 Power Supply and mounting bracket	7. LO/HI speed selection icon buttons
2. Power connector	8. Saline pump icon button
3. Blue activation button	9. Guidewire lock indicator light
4. Carriage to advance and retract driveshaft	10. Guidewire clamp
5. Saline infusion tubing set	11. Diamond-coated spheres on driveshaft
6. Saline tubing connector	12. Distal tip of driveshaft

Figure 2-5: FreedomFlow™ Orbital Atherectomy System - Electric[1]

2.3 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. The driveshaft of User Handles H3001 and H6002 have 5 diamond coated spheres with the largest sphere 2 mm in diameter. The

[1] Item 1 is the reusable Power Supply. User Handle and Saline Infusion Tubing Set are listed as Items 2-12.

driveshaft of User Handles H4001 and H6001 have 5 same size (1.5 mm in diameter) diamond coated spheres.

H4001 and H6001 – 5 French compatible

H3001 and H6002 – 6 French compatible

Figure 2-6: Driveshaft Configurations

2.4 INTENDED USE

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

2.5 INDICATION FOR USE

The FreedomFlow™ Orbital Circumferential Atherectomy System is indicated to remove atherosclerotic plaque and modifying vessel wall compliance within peripheral arterial vessels. The therapy is intended for patients who are acceptable candidates for percutaneous transluminal atherectomy.

3 STUDY PURPOSE AND OBJECTIVE

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

4 STUDY DESIGN

4.1 OVERVIEW

The FAST II study is a prospective, multi-center, non-randomized single-arm study designed to evaluate the safety and effectiveness of the FreedomFlow™ Orbital Circumferential 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 112 subjects and will be conducted at up to 15 investigational sites in the United States. Approximately 56 subjects will be enrolled using the pneumatic system and 56 subjects will be enrolled using the electric system.

4.3 STUDY DURATION

Enrollment is expected to take approximately 12 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 EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is technical Success defined as the ability of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System to achieve a residual diameter stenosis ≤50% without adjunctive therapy, as assessed by an independent Angiographic Core Laboratory.

5.2 PRIMARY SAFETY ENDPOINT

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

The components of the MAE are defined as:

1. **Cardiovascular related death:** All cardiovascular cause mortality.
2. **Myocardial infarction (MI):** Any newly diagnosed MI post procedure, defined as CK-MB ≥2X upper limit normal (ULN).
3. **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.
4. **Clinically significant target vessel dissection:** NHLBI grade C or greater as confirmed by angiography.
5. **Clinically significant target vessel perforation:** NHLBI Type III as confirmed by angiography.
6. **Unplanned major target limb amputation:** Amputation of the transmetatarsals or higher that was not previously planned as part of the overall treatment strategy.

7. **Clinically relevant distal embolization:** Emboli requiring surgical or medical intervention and/or the presence of symptoms.
8. **Pseudoaneurysm:** disruption/weakening of the arterial wall at the treatment site as confirmed by angiography.

5.3 SECONDARY ENDPOINTS

1. Clinical success, defined as ≤50% residual stenosis at target lesion with or without adjunctive therapy, as assessed by an independent Angiographic Core Laboratory.

2. Procedure success, defined as ≤50% residual stenosis at target lesion with or without adjunctive therapy, no procedure-related MAE, no device malfunction causing the procedure to be aborted.

3. Improvement of ABI at 30 days and 6 months.

4. Improvement of Rutherford Classification at 30 days and 6 months.

5. Improvement of patient reported outcomes (PRO, VascuQoL questionnaire) at 30 days and 6 months.

6. Clinically driven target lesion revascularization (TLR) at 6 months, target vessel revascularization (TVR) at 30 days and 6 months (as assessed by an independent Angiographic Core Laboratory).

7. Primary patency, primary assisted patency and secondary patency at 30 days and 6 months. Patency will be evaluated by duplex ultrasound and evaluated by an independent Vascular 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. Objective hemodynamic evaluation that subject has a resting ankle-brachial index (ABI) ≤ 0.90 **OR** a resting toe-brachial index (TBI) of ≤ 0.80 **OR** ankle pressure of ≤70 mmHg.
4. Clinical presentation of lifestyle limiting claudication, rest pain and/or ischemic wound as characterized by Rutherford Classification 2, 3, 4, or 5.
5. Disease is located in the common femoral, superficial femoral, popliteal, tibioperoneal, anterior tibial, posterior tibial, or peroneal arteries.
    a. De novo target lesion(s) with stenosis ≥70% by visual estimation and/or
    b. Lesion(s) treated by percutaneous transluminal angioplasty (PTA) and/or atherectomy ⩾ 3 months prior with a restenosis ⩾70% by visual estimation.
    c. Up to three lesions can be treated at the index procedure provided the cumulative total lesion length is ⩽ 20 cm AND all lesions are in the same target leg.
6. Target reference vessel diameter (proximal and distal to target lesion) is 2 to 8 mm by angiographic visual estimation.
7. At least one patent vessel run-off to the ankle or foot at baseline.
8. The target lesion(s) can be successfully crossed with a commercially available 0.014" atherectomy guidewire without any complications during wiring procedure.
9. 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. Target lesion is a Chronic total occlusion (CTO) with occlusion length greater than 10 cm and/or with wire crossed sub-intimally. CTO wire placement in true lumen must be confirmed via IVUS prior to enrollment.
5. Subject has significant stenosis or occlusion of inflow tract (upstream disease) not successfully treated during the index procedure or prior to treatment of the target lesion.

6. 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.
7. Evidence or history of aneurysmal target vessel.
8. Clinical/angiographic evidence of distal embolization prior to intervention.
9. History of an endovascular procedure or open vascular surgery on the index limb within 30 days prior to the index procedure (other than treatment of inflow tract disease). Endovascular procedure or open vascular surgery on the non-index limb cannot be staged within 2 weeks prior to the index procedure.
10. Planned endovascular or surgical procedure prior to the patient's 30 day follow up.
11. Signs and symptoms of systemic infection (temperature of $\geq$ 38.0° Celsius and WBC of $\geq$ 12,000 cells/μL) at the time of assessment;
    Note: If infection is adequately treated and controlled patient may be enrolled.
12. Unstable coronary artery disease or other comorbid condition(s) that, in the judgment of the physician precludes safe percutaneous intervention.
13. Significant acute or chronic kidney disease with a creatinine level > 2.5mg/dL and/or requiring dialysis.
14. Evidence or history of intracranial or gastrointestinal bleeding, intracranial aneurysm, myocardial infarction or stoke within 2 months of index procedure.
15. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.
16. Subjects in whom anti-platelet, anticoagulant, or thrombolytic therapy is contraindicated.
17. Heparin-induced thrombocytopenia (HIT) not able to use Bivalirudin.
18. Uncorrectable bleeding diathesis, platelet dysfunction, thrombocytopenia with platelet count less than 125,000/mm^2, known coagulopathy, or INR > 1.8.
19. Evidence of thrombus within target lesion or thrombolytic therapy within 2 weeks of the index procedure.
20. Has life expectancy < 12 months in the opinion of the investigator.
21. Subject is unwilling or unable to comply with the follow-up study requirements.
22. Subject is currently participating in an investigational drug or another investigational device exemption (IDE) study.

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 the investigational device is attempted. A 25% enrollment ceiling per site will be implemented.

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 and core lab)
- Duplex Ultrasound (if available, recorded and sent to sponsor and core lab)
- Rutherford Classification
- Laboratory Assessments:
    - CBC, creatinine, and potassium
    - 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)
- VascuQoL Questionnaire

- Ankle Brachial Index (ABI) and/or Toe Brachial Index (TBI)
- 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

Prior to or up to the time of the index procedure, 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 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.
- Following treatment of any lesions that are pre-dilated by balloon angioplasty if performed.
- After the Cardio Flow FreedomFlow™ orbital circumferential 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 Lesion Intervention

If a non-target lesion(s) is located at the iliac artery or at the femoral artery with a vessel size greater than 8 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 Cardio Flow FreedomFlow™ orbital circumferential atherectomy procedure. The Cardio Flow FreedomFlow™ orbital circumferential atherectomy procedure can be performed ONLY if there are no angiographic complications at the non-target vessel/lesion site or in downstream

vasculatures, and no observed clinical adverse events. If any angiographic complication at the non-target vessel/lesion site and/or downstream vasculatures or a clinical adverse event occurred, the subject MUST not proceed to the Cardio Flow FreedomFlow™ orbital circumferential atherectomy procedure. The subject will be considered as an angiographic screening failure.

If a non-target lesion(s) located at the target limb does not require an immediate attention, it can be staged and treated with any commercially available devices greater than 30 days post the index procedure after the 30-day study assessment.

If a non-target lesion(s) is at non-target limb, it may be treated either at least a week prior to the index procedure without on-going adverse event at the time of enrollment or 30 days post the index procedure after the 30-day study assessment.

6.5.3 Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy Procedure

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

Performing the Atherectomy Procedure

Interventionalist will place commercially available 0.014-inch 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.

4. Select the appropriate speed for the vessel size.

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. Depress the blue activation button to initiate rotation and maintain selected speed.

6. Once rotation is started, slowly advance the 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 antispasm 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 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.

<u>Removal of the User Handle and Driveshaft</u>

1. Release blue activation button to stop rotation and retract driveshaft proximal to the lesion using the 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 pump by tapping the Pump icons.

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 pump is turned off during a procedure, power to the User Handle will cease immediately.

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

2. Turn off pump by tapping the Pump icons .

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 units heparin, 3000 µg nitroglycerin and 2.5mg Cardizem) can be infused intra-arterially at a rate of 6 to 7 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
- 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 and/or TBI
- Duplex ultrasound of treated lesion per Vascular Ultrasound Core Laboratory 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 and/or TBI
- Duplex ultrasound of treated lesion per Vascular Ultrasound Core Laboratory 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	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
Angiography	X[a]	X		X[b]	X[b]
Duplex Ultrasound	X[c]			X	X
Medications	X		X	X	X
Adverse Events	X	X	X	X	X

[a] Baseline angiography will be performed at the beginning of index procedure.

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

[c] 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 Circumferential 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 STATISTICAL METHODS AND ANALYSIS

The study is designed as a prospective, multi-center, nonrandomized single arm study to evaluate the safety and effectiveness of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System for atherosclerotic plaque removal and vessel compliance modification in *de novo* native target lesions in the peripheral vasculature of the lower extremities.

8.1 DETERMINATION OF SAMPLE SIZE

The sample size is calculated to simultaneously power for the primary effectiveness and primary safety endpoints by comparison to the pre-specified Performance Goal (PG).

Primary Effectiveness Endpoint

Sample size estimates were calculated for the primary effectiveness outcome by comparing the technical success rate to the pre-specified performance goal of 86% The performance goal of 86% was derived using a random effect meta-analysis based on the technical success rates that were obtained from the results of recent atherectomy studies (See Table 8-1 below) and an allowed 10% margin. The underlying technical success rate was assumed 96%.

The hypotheses are:

H_0: technical success rate $\leqslant$ 86%

Ha: technical success rate > 86%

Under an exact, one-sided test for a single binomial proportion, at the 0.025 significance level, a sample size of 101 mITT subjects will be required to provide 90% power to meet this technical success endpoint.

Table 8-1: Technical Success Rates

Study	N	Success	Technical Success Rate
Davis et al 2017[25]/IFU (Phoenix)[26]	123	117	95.1%
Roberts et al 2014[27] (SilverHawk)	131	121	92.4%
Zeller et al 2009[28] (Pathway)	210	208	99.1%
Weighted Average (95% CI)	96% (90%, 99%)		

Primary Safety Endpoint

Literature review and a random effect meta-analysis showed a 95% freedom from MAE at 30 days. The pre-specified performance goal for the primary safety endpoint is 85% and was derived using a random effect meta-analysis based on the Freedom of MAE rates from recent atherectomy studies and an allowed 10% margin.

The hypotheses are:

H_0: Freedom from MAE at 30 days $\leqslant$ 85%

Ha: Freedom from MAE at 30 days > 85%

Under an exact, one-sided test for a single binomial proportion at the 0.025 significance level, a sample size of 102 mITT subjects will be required to provide at least 90% power to meet this primary safety endpoint.

Table 8-2: Freedom from MAE Rates

Study	N	MAE Event	Freedom from MAE Rate
Davis et al 2017[25]/IFU (Phoenix)[26]	105	6	94.29%
Roberts et al 2014[27] (SilverHawk)	131	9	93.13%
Safian et al 2009[29] (Diamondback)	124	4	96.77%
NCT01937351[30] (Pantheris)	130	9	93.08%
Dipple et al 2015[31] (Turbo-Power Laser/PTA)	167	9	94.61%
Zeller et al 2017[32] (DA+DCB)	48	1	97.92%
Zeller et al 2009[28] (Pathway)	172	2	98.84%
Weighted Average (95% CI)	95% (93%, 97%)		

Overall Sample Size

In order to adequately power for both primary effectiveness and primary safety hypotheses, we require a sample size of 102 mITT subjects who complete 30 days follow-up. The dropout rate

of mITT subjects is assumed to be 10 %. The final sample size for the study will be 112 subjects.

8.2 ANALYSIS SETS

The primary analysis for effectiveness and safety will be based on a modified intent-to-treat principle. The per-protocol analysis set is designated as supportive.

Intent-to-Treat (ITT): the ITT set will be comprised of all subjects who have signed informed consent, meet all the inclusion and none of the exclusion criteria.

Modified Intent-to-Treat (mITT): the mITT set will be comprised of all ITT subjects who have the investigational device attempted.

Per-Protocol (PP): the PP set will be comprised of all subjects in the mITT set who have no major protocol deviations. All major protocol deviations will be reviewed and finalized before the data lock for final analysis.

8.3 STATISTICAL ANALYSIS

General Statistical Consideration

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.1 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software. It is planned that the data from all sites that participate in this protocol will be combined for analysis.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values. Unless otherwise specified, the analyses will be performed using descriptive statistics.

A statistical analysis plan (SAP) accompanies this protocol and should be referred to for further information on intended statistical methods; the SAP will be finalized and approved prior to study database lock. The SAP will detail the analytical methodology and assumptions beyond those presented below.

Anaysis of Primary Endpoints

The study will be considered a success if both primary effectiveness and safety objectives are met using the mITT Set at the one-sided 0.025 level of significance in the final analysis.

Analysis of Primary Safety Endpoint

The analysis of primary safety endpoint (i.e., freedom from MAE at 30 days) will be performed in the mITT analysis set. The primary safey will be assessed by calculating the proportion of subjects who have no MAE at 30 days aggregated over the mITT subjects. A 95% two-sided confidence interval will be estimated using the Clopper-Pearson interval (F-distribution method).

In case of missing data that is of concern at 30 days when the primary safety endpoint is evaluated, the probability of a subject achieving freedom from MAE at 30 days will be estimated using Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. The Kaplan-Meier estimate and its 95% log-log confidence interval will be constructed from the day of index procedure through the 30 days follow-up. For subjects with MAE, days of follow-up will be computed as the days from the index procedure to the onset date of the first event. For subjects without MAE, days of follow-up will be computed as the days from the index procedure to the last follow-up at the time of data lock for primary analysis.

If the lower bound of this 95% confidence interval is greater than the performance goal 85%, we can conclude that the primary safety endpoint is met.

As a sensitivity analysis, a tipping-point analysis will be conducted. A tipping point is defined as the number of events in the missing cohort at which the study conclusion is changed. Let n_m be the number of missing values in the mITT cohort. Starting at 0 and ending at n_m , the event rate is changed by adding 1 event at a time. The 95% confidence interval will be calculated each time when adding 1 event.

The primary safety analysis will also be performed in the PP set as supportive evidence.

Analysis of Primary Effectiveness Endpoint

The primary effectiveness will be assessed by calculating the proportion of subjects who have achieved technical success over the mITT subjects. A 95% two-sided confidence interval will be estimated using the Clopper-Pearson interval (F-distribution method). If the lower bound of this 95% confidence interval is greater than the performance goal 86%, we can conclude the primary effectiveness endpoint is met.

The primary effectiveness analysis will also be performed in the PP set as supportive evidence.

<u>Analysis of Secondary Endpoints</u>

The secondary endpoints will be analyzed with descriptive statistics; there will be no formal statistical hypothesis test. Details of these statistical analyses will be provided in a separate standalone Statistical Analysis Plan.

<u>Poolability of Investigational Sites</u>

This study is designed and conducted as a multicenter clinical trial. Data from all the sites will be pooled. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results.

A Chi-Square test will be conducted to investigate the overall homogeneity across all sites for the primary safety and effectiveness endpoints. The tests will be conducted at the two-sided 0.15 level of significance. If the p-value is less than 0.15 then further evaluation is warranted. In addition, a graphical display of the proportions of primary safety and effectiveness success along with 95% confidence intervals for each site will be constructed. The confidence intervals will be constructed using the Clopper-Pearson interval (F-distribution method) and be plotted relative to the performance goal. Sites with fewer than 5 subjects will be first combined into an adjacent single super-site that shares similar site characteristics for these analyses. The site characteristics will be determined before data lock for statistical analysis. Two sets of poolability analyses will be conducted, one is to use all sites without any combination, the other is to combine small sites into a super-site which has similar characteristics. If the sites are not poolable, we will conduct a random effect model to determine its effect on the primary endpoints.

In addition to the homogeneity test for the primary endpoint, other variables such as baseline demographics and lesion characteristics will also be compared across sites to assess the appropriateness of pooling data from across all sites.

Analysis of Adverse Events (AE)

For AE reporting, the primary analysis will be based on subject counts. A subject with more than one event will be counted only once toward the event rate based on the total number of subjects with AEs. An event count will also be presented. For example, if a subject experiences one major unplanned amputation of the treated limb and two clinically-driven TLRs within 30 days, the subject will be counted once in the rate of total subjects with a 30-day MAE; the same subject will be counted once in the individual event category of “Major Unplanned Amputation of the Treated Limb” and twice in the “Clinically-Driven TLR” category.

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 “XX-YYY” where:

XX = 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 or site research personnel 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

A 30-day primary endpoint report summarizing all relevant observations will be prepared following receipt of all monitored subject data forms. The 30-day primary endpoint report will be submitted to FDA in support of 510(k) clearance.

Subjects will continue to be followed for 6 months and 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.

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.) Study closure visits will be conducted by trained monitors or designees.

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 ADMINISTRATIVE 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 the investigator and by the core laboratory.

Angiographic and Vascular Ultrasound Core Laboratory Protocols shall be provided to the investigational sites.

12.2 CLINICAL EVENT COMMITTEE

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the trial. An independent CEC will be utilized for this study. The CEC will be responsible for adjudicating the seriousness and relatedness of all endpoint events and serious device and/or procedure related adverse events occurring during the study period. The CEC will meet regularly. All available data (including lab reports, films, discharge reports, etc.) will be available to adjudicate the events. The committee will also review and rule on all deaths that occur throughout the trial. The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

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;
- Key correspondences 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	Reporting Time Frame
UADE	Sponsor, EC/IRB	As soon as possible but no later than 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	Sponsor, EC/IRB	As soon as possible but no later than 5 working days of knowledge

Type of Report	Prepared by PI for	Reporting Time Frame
or physical well-being of a subject in an emergency)		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.		

Table 12-2 lists those reports that are the sponsor's responsibility and timelines to report to the FDA and reviewing ECs/IRBs.

Table 12-2: Sponsor Reporting Responsibility

Type of Report	Report to	Reporting Time Frame
UADE	FDA and all ECs/IRBs	Within 10 working days from the time the Sponsor first learns of the
Withdrawal of IRB/EC Approval or other action on part of the IRB/EC that affects the study	FDA, all ECs/IRBs, and all investigators	Within 5 working days after receipt of the withdrawal of approval.
Withdrawal of FDA approval	all ECs/IRBs and all investigators	Within 5 working days after receipt of notice of the withdrawal of FDA approval.
Current investigator list	FDA	At 6-month intervals. Submit the first list 6 months after FDA approval.
Device Recall	Investigators, ECs/IRBs and FDA	Within 30 working days after the request is made.
Progress Reports	ECs/IRBs and FDA	At least yearly.
Inappropriate Informed Consent	FDA	Investigator's report submitted within 5 working days of receipt of notice of such use.
Study Closure	ECs/IRBs and FDA	Within 30 working days of the completion or termination of the investigation.
Final Report	Investigators, ECs/IRBs and FDA	Within 6 months of study closure.

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 and dated Clinical Trial Agreement
- Signed and dated Investigator Agreement
- Signed and dated Protocol Signature Page
- 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

The data and results from the study are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical study. The Investigators will not use the clinical study/investigation-related data without the written consent of the Sponsor for any other purpose than for clinical study/investigation completion or for generation of publication material, as referenced in the Clinical Trial Agreement/Investigator Agreement.

The Sponsor acknowledges that the study Investigators intend to publish the results of the clinical investigation. The Sponsor shall use all reasonable efforts to collaboratively ensure the appropriate publication or dissemination of the conclusions of the study, and Investigators shall not publish results derived from their institution until the combined results from the entire investigation has been published in a joint, multi-center publication.

Sponsor must receive any proposed publication and/or presentation materials for publications at least 30 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement/Investigator Agreement.

The Sponsor is responsible for registering the Clinical Investigation on www.clinicaltrials.gov. Institution(s) and/or Principal Investigator(s) shall not take any action to register the study.

13 REVISION HISTORY

Date	Description
18-JUN-2018	Initial release, Version A
14-SEP-2018	Version B. Per FDA's recommendations, following sections have been updated. 1. Added a primary effectiveness endpoint – Technical Success and a hypothesis test for the primary effectiveness endpoint. 2. Updated the primary safety endpoint – Freedom from MAE at 30 days and the hypothesis test for the primary safety endpoint. 3. Updated the sample size per hypothesis test. 4. Included an enrollment ceiling per site. 5. Updated statistical analysis section. 6. Modified Inclusion Criteria #5 and Exclusion Criteria #9 and 10 for clarity.
07-MAR-2019	Version C. Per site-requested clarifications, the following sections have been updated. 1. Modified Exclusion Criteria #5, 9, and 11 for clarity.
25-SEP-2019	Version D. The following sections have been updated. 1. Modified Components of MAE definition #4, #5, to remove ambiguities. 2. Modified Inclusion Criteria #5b for clarity, #5c to align with other published studies. 3. Modified Exclusion Criteria #4 to align with other published studies and #19 for clarity.
01-NOV-2019	Version E. The following sections have been updated. 1. Modified Components of MAE definition #4, #5 back to Revision C wording.

01-APR-2020	Version F. The following sections have been updated. 1. Added Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System – Electric to the investigation list. 2. Added device descriptions of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System - Electric. 3. Clarified sample size allocations. 4. Increased investigational site to 15. 5. Clarified procedure for performing the atherectomy using either pneumatic or electric system.

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