FARAPULSE

PersAFOne:

Feasibility Study of the
FARAPULSE™ Endocardial Multi Ablation System in the Treatment
of
Persistent Atrial Fibrillation

CLINICAL INVESTIGATION PLAN (CIP) NUMBER: CS0607 REVISION E

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Revision History

Revision	Change Description
A	**Initial Release**
B	**Updated to Reflect Change of System Name**
C	**Correction of typographical errors throughout document**
D	**Skipped for administrative purposes**
E	• **Added use of amiodarone after day of index ablation procedure as an additional exclusion criterion (exclusion criteria #14)** • **Updated clinical experience data for prior clinical investigations** • **Added total fluoroscopy dose as an assessment in addition to exposure time** • **For women of childbearing potential, a pregnanacy test added to 6 and 12 mo follow-up visits, in the event that fluoroscopic examination of diaphragm is required** • **Added revision history table** • **Updates to syntax throughout document for clarity**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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Executive Summary

SPONSOR NAME:	FARAPULSE, Inc.
FULL TITLE OF STUDY:	Feasibility Study of the FARAPULSE™ Endocardial Multi Ablation System in the Treatment of Persistent Atrial Fibrillation
SHORT TITLE OF STUDY:	PersAFOne (pronounced per-'se-fa-nē)
PROTOCOL NUMBER:	CS0607, Revision E
OBJECTIVE:	The objective of this safety and feasibility study is to assess whether the endocardial creation of electrically nonconductive lesions via PEF catheter ablation applied using the FARAPULSE Endocardial Multi Ablation System is a feasible and safe treatment for PersAF and associated AFL
CLINICAL HYPOTHESIS:	Endocardial creation of electrically nonconductive lesions in cardiac tissue via PEF catheter ablation using the FARAPULSE Endocardial Multi Ablation System is a feasible and safe treatment for PersAF.
NAME OF INVESTIGATIONAL DEVICES:	FARAPULSE Endocardial Multi Ablation System • FARAWAVE™ Endocardial Ablation Catheters • FARAFLEX™ Endocardial Ablation Catheter • FARASTAR™ Endocardial Generator System • FARADRIVE™ Deflectable Sheath
STUDY OVERVIEW:	This is a prospective, multi-center safety and feasibility study in subjects with persistent AF. Subjects will undergo percutaneous PEF ablation for pulmonary vein isolation as well as cavotricuspid isthmus interruption and other left atrial ablations at the investigator's discretion. Subjects will then be followed at 30 days, 75 ± 15 days, 6 months and 12 months for adverse events, recurrence of arrhythmia after a 90 day blanking period and other relevant outcome measures.
STUDY POPULATION	Subjects with documented symptomatic persistent AF (AF duration 7 – 365 days) and a 24-hour Holter monitor showing continuous AF within 90 days prior to the enrollment date; who are refractory or intolerant to at least one Class I/III antiarrhythmic agent.
PLANNED ENROLLMENT:	Up to 40 subjects
CLINICAL SITES:	Up to 4 clinical sites in Europe

DURATION OF PARTICIPATION:	Subjects will be followed at 30 days, 75 days, 6 months and 12 months with a 90-day Blanking Period for recurrent atrial fibrillation, atrial flutter or atrial tachycardia following the Index Procedure. Reablation with the study device(s) during the Blanking Period is permitted but does not extend either the Blanking Period or the total follow-up interval. The enrollment period is estimated to take 9 months and subjects will be followed for up to 12 months. The total study duration will be approximately 21 months.
PLANNED PROCEDURE:	Index Procedure: • Subjects will undergo an attempt to isolate all pulmonary veins or their anatomic equivalent. • Subjects with a past history of atrial flutter, who are at risk of atrial flutter, who present with atrial flutter during the Index Procedure or who have inducible cavotricuspid isthmus-mediated (typical) flutter may undergo ablation of the cavo-tricuspid isthmus at the discretion of the investigator. • Additional left atrial lesions may be made at the discretion of the investigator including focal sites, electrical gaps and lines of isolation. 75-Day Remap Procedure: • Subjects will undergo a remapping procedure at 75 ± 15 days to assess the durability of the ablation lesions performed during the Index Procedure. • During this procedure, additional ablations may be made at the discretion of the investigator to optimize patient outcomes.

PRIMARY SAFETY ENDPOINT:	The primary safety endpoint for this study is the Composite Safety Endpoint (CSE) defined as the incidence of the following early-onset and late-onset serious adverse events (SAEs) which are device- or procedure-related, as adjudicated by the CEDMC. (See **Table 4. Composite Safety Endpoint Definitions in Section 6.1**). <u>Early onset (within 30 days of an Index or Remap Procedure)</u> • Death • Myocardial infarction (MI) • Persistent diaphragmatic paralysis • Stroke or transient ischemic attack (TIA) • Peripheral or organ thromboembolism • Pericarditis • Cardiac tamponade / perforation • Vascular access complications requiring intervention • Heart block <u>Late onset (any time during follow-up through 12 months)</u> • Pulmonary vein (PV) stenosis (> 70% diameter reduction from baseline) • Atrio-esophageal fistula
SECONDARY SAFETY ENDPOINTS:	1. The Primary Safety Endpoint assessed at 7 days 2. The proportion of subjects with a device- or procedure-related SAE 3. The proportion of subjects with stroke or TIA 4. The proportion of subjects requiring cardioversion 5. The proportion of subjects requiring an arrhythmia-related (AF, AFL or AT) hospitalization
PRIMARY FEASIBILITY ENDPOINT:	The proportion of subjects that achieve Acute Procedural Success (APS) defined as the percutaneous endocardial creation of a complete, electrically isolating set of lesions around the ostia of the pulmonary veins (PVI) using the FARAPULSE Endocardial Multi Ablation System during the Index Procedure, as clinically assessed by entrance and/or exit block performed ≥ 20 minutes after the last PVI lesion is made.

SECONDARY FEASIBILITY ENDPOINTS:	1. The proportion of subjects who undergo the protocol-specified 75-Day Remapping Procedure and achieve Chronic Procedural Success (CPS) defined as persistent electrical isolation of all initially ablated pulmonary veins. Chronic Procedural Success will be subdivided by Index Procedure only CPS and Reablated CPS subjects. 2. The proportion of attempted subjects that achieve Acute CTI Success, defined as the creation of bi-directional electrical block across the cavotricuspid isthmus using the investigational devices using the FARAPULSE Endocardial Multi Ablation System during the Index Procedure. 3. Durability of the CTI and/or other extra-PV lesion set(s), when applicable. Durability is defined as unaltered integrity of each such lesion assessed at the Remapping Procedure. 4. The proportion of subjects that achieve Therapeutic Success, defined as freedom from: a. Post Blanking Period through assessment: occurrence of AF, AFL or AT or ablation for AF/AFL/AT using the study device b. At any time: ablation for AF/AFL/AT with a nonstudy device Therapeutic Success will be assessed from the end of the 90-day Blanking Period through Months 6 and 12 and will be subdivided by on / off AFDs (Atrial Fibrillation Drugs) post-Blanking Period.
ADDITIONAL ASSESSMENTS:	1. Proportion of subjects with early recurrence of atrial fibrillation (ERAF) by 90 days after the Index Procedure. 2. Time to Therapeutic Failure. 3. Proportion of all ablated pulmonary veins that are isolated at the Index Procedure using the study device. 4. Proportion of all ablated pulmonary veins isolated using the study device during the Index Procedure that remain isolated at the 75-day remapping procedure. 5. The proportion of attempted subjects that achieve Chronic CTI Success, defined as persistent bi-directional electrical block across the CTI assessed at the 75-day Remapping Procedure. 6. The proportion of attempted subjects that achieve Chronic Focal Success, defined as persistent electrical nonconductivity of all extra-PV tissue targeted for ablation in the Index Procedure, excluding the CTI.

PROCEDURAL ASSESSMENTS:	1. Assessments of duration for procedure components a. Procedure time (initiation of venous access to venous access closure) b. Dwell time (sum of catheter entry-to-exit durations for each cardiac chamber) c. Total ablation time (first ablation to last ablation) d. Fluoroscopy time and dose (total duration and dose of exposure) 2. Characterization of lesion sets a. PVI ablations b. Extra-PV ablations, excluding CTI ablations c. CTI ablations d. Anomalous PV ablations
INCLUSION CRITERIA	Study subjects are required to meet all the following inclusion criteria to participate in this study: 1. Patients with documented drug-resistant symptomatic persistent AF meeting all three of the following criteria: a. Patient is refractory or intolerant to at least one Class I/III antiarrhythmic agent. b. ECG-documented first episode of persistent AF, lasting longer than 7 days but not longer than 365 days c. Holter within 90 days prior to the Enrollment Date demonstrating 24 hours of continuous AF 2. Patients who are ≥ 18 and ≤ 75 years of age on the day of enrollment. 3. Patient participation requirements: a. Lives locally b. Is willing and capable of providing Informed Consent to undergo study procedures c. Is willing to participate in all examinations and follow-up visits and tests associated with this clinical study.

EXCLUSION CRITERIA	Subjects will be excluded from participating in this study if they meet any one of the following exclusion criteria: 1. AF that is: a. Paroxysmal (longest AF episode < 7days) b. Longstanding (has persisted > 12 months or that does not respond to cardioversion if < 12 months) c. Secondary to electrolyte imbalance, thyroid disease, alcohol abuse or other reversible / non-cardiac causes 2. Left atrial anteroposterior diameter ≥ 5.5 cm as documented by transthoracic echocardiography (TTE) or computed tomography (CT) 3. Any of the following cardiac procedures, implants or conditions: a. Clinically significant arrhythmias other than AF, AFL or AT b. Hemodynamically significant valvular disease c. Prosthetic heart valve d. NYHA Class III or IV CHF e. Previous endocardial or epicardial ablation or surgery for AF f. Atrial or ventricular septal defect closure g. Atrial myxoma h. Left atrial appendage device or occlusion i. Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices j. Significant or symptomatic hypotension k. Bradycardia or chronotropic incompetence l. History of pericarditis m. History of rheumatic fever n. History of congenital heart disease with any residual anatomic or conduction abnormality 4. Any of the following within 3 months prior to enrollment: a. Myocardial infarction b. Unstable angina c. Percutaneous coronary intervention d. Heart surgery (e.g. coronary artery bypass grafting, ventriculotomy, atriotomy) e. Heart failure hospitalization f. Stroke or TIA g. Clinically significant bleeding h. Pericarditis or pericardial effusion i. Left atrial thrombus 5. History of blood clotting or bleeding abnormalities.

EXCLUSION CRITERIA (CONTINUED)	6. Contraindication to, or unwillingness to use, systemic anticoagulation 7. Contraindications to CT or MRI 8. Sensitivity to contrast media not controlled by premedication 9. Women of childbearing potential who are pregnant, lactating or not using birth control 10. Medical conditions that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or confound data or its interpretation, including but not limited to a. Body mass index (BMI) > 40 b. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant c. Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or significant dyspnea d. Renal insufficiency with an estimated creatinine clearance < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant e. Active malignancy or history of treated cancer within 24 months of enrollment f. Clinically significant gastrointestinal problems involving the esophagus, stomach and/or untreated acid reflux g. Clinically significant infection h. Predicted life expectancy less than one year 11. Clinically significant psychological condition that in the investigator's opinion would prohibit the subject's ability to meet the protocol requirements 12. Current or anticipated enrollment in any other clinical study 13. Employment by FARAPULSE or the same hospital department or office of any investigator, or a family member of any of the preceding groups. 14. Use of amiodarone after day of index ablation procedure. Patients will cease use of amiodarone on or before the date of the index ablation procedure.

Abbreviations and Acronyms

ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse Event
AF	Atrial fibrillation
AFD	Atrial Fibrillation Drug
AFL	Atrial flutter
APS	Acute Procedural Success
AT	Atrial tachycardia
BMI	Body Mass Index
CA	Competent Authority
CBC	Complete blood count
CEDMC	Clinical Events and Data Monitoring Committee
CHA_2DS_2-VASc	Termed "CHADS-VASC" a clinical prediction rule for stroke
CHF	Congestive heart failure
CIP	Clinical Investigation Plan
CPS	Chronic Procedural Success
CRF	Includes CRF (case report form) and eCRF (electronic case report form)
CRO	Clinical research organization
CSE	Composite Safety Endpoint
CT	Computed tomography
CTI	Cavotricuspid isthmus
DCCV	Direct current cardioversion
EC	Ethics Committee
ECG	Electrocardiogram
ERAF	Early recurrence of atrial fibrillation
ICF	Informed Consent Form
INR	International normalized ratio
IVC	Inferior vena cava
LA	Left atrium or left atrial
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal atrial fibrillation
PersAF	Persistent atrial fibrillation
PEF	Pulsed electric field
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Pulmonary vein
PVI	Pulmonary vein isolation
PVS	Pulmonary vein stenosis
SADE	Serious adverse device effect
SAE	Serious adverse event
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack

TTE	Transthoracic echocardiography
TTM	Transtelephonic monitor
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect

1. Introduction

1.1 Background and Rationale

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 2.2 million people in the United States and 4.5 million in the European Union.[1, 2]. The incidence increases with advancing age, affecting 6% of the population over age 60 and 10% of the population over age 80[3, 4]. Age-adjusted population trending projects 16 million people in the United States will have AF by 2050[5]. Atrial fibrillation remains a significant cause of morbidity and mortality in industrialized societies. The annual risk of AF related stroke is 5% per year and one of every six strokes diagnosed occurs in the presence of AF.[6] Therefore, patients with AF require long-term anticoagulation to prevent embolic events. Failure to manage AF may also lead to anatomic and electrical remodeling of the left atrium, tachycardia-induced cardiomyopathy, and reduced left ventricular function (heart failure). AF remains an extremely costly public health burden, with annual per patient cost of care approaching €3000 (approximately U.S. $3200).[7]

The Heart Rhythm Society (HRS) 2017 Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[8] defines several different stages of atrial fibrillation.

- Paroxysmal AF (PAF): AF that terminates spontaneously or with intervention within 7 days of onset.
- Persistent AF (PersAF): continuous AF that is sustained beyond 7 days.
    - Long-standing persistent AF: continuous AF of greater than 12 months' duration.
    - Permanent AF: the presence of [persistent] AF that is accepted by the patient and physician, and for which no further attempts to restore or maintain sinus rhythm will be undertaken.

Catheter ablation for the treatment of PAF is increasingly being performed as first line therapy for PAF and clinical evidence is accruing that this may well become an accepted first line treatment.

Catheter ablation for the treatment of PersAF is complicated by the heterogeneity of the underlying pathophysiologic mechanisms and the generally reduced efficacy of ablation for continuous AF states. A small study of catheter ablation vs. antiarrhythmic drug treatment of PersAF found a significant advantage of ablation over AFDs. [9] While no catheter system has received FDA or CE Mark labeling to date, several single arm clinical investigations seeking device approvals for this indication are under way.

1.2 Irreversible Electroporation (IRE)

Al-Sakere 2007[10] described irreversible electroporation as a non-thermal tissue ablation technique in which intense short duration electrical fields are used to permanently open pores in cell membranes, thus producing non-thermal tissue ablation. Their study, using a mouse model, showed complete regression in 92% of treated tumors. IRE ablation has a tissue specific mechanism of ablation. The tissue injury from IRE ablation occurs at the cellular level with loss of homeostasis leading to necrosis or

apoptosis.[11 12 13 14] IRE ablation typically spares the extracellular matrix, which facilitates rapid wound healing.[15, 16, 17, 18, 19]

Thomson 2011[20] reported a case-series study (N=38) assessing the safety of IRE for treating liver, kidney or lung cancers in humans. The first four patients showed signs of transient ventricular arrhythmia, so subsequent patients were all treated using electrocardiogram (ECG)-synchronized deliver of electroporation pulses. There were two further arrhythmias, and two cases of inadvertent damage to neighboring organs. 68% of tumors were completely ablated. The authors concluded that IRE is safe for clinical use, provided ECG-synchronized delivery is used.

A research group led by FHM Wittkampf in Utrecht has been investigating the potential effectiveness and safety of epicardial electroporation in AF ablation procedures using porcine models. Wittkampf 2011[21] (N=10) used a circular ablation catheter and showed that PVI was achieved in all animals, with no sign of stenosis at 3-week follow up. Van Driel 2014[22] (N=6) confirmed this result out to 3-month follow up. Neven 2014[23] (N=5) showed that electroporation lesion depth depended on the level of electrical energy applied, reaching 8 mm at 300 joules.

Van Driel 2015 (N=20) showed that electroporation could create deep lesions close to the phrenic nerve without damage to the nerve. Neven 2014 similarly showed that neighboring coronary arteries were undamaged by electroporation (N= 5). These animal studies suggest that irreversible electroporation can safely create deep lesions in heart tissue when applied epicardially without harming adjacent tissues.

1.3 Summary of FARAPULSE Clinical Studies

1.3.1 Endocardial Ablation Studies – The IMPULSE Study

FARAPULSE, Inc. initiated a safety and feasibility study at Na Homolce Hospital in Prague, Czech Republic and Hopital Cardiologique du Haut-Leveque in Pessac, France under the "IMPULSE" Protocol, CS0188. This study is being conducted using the FARAPULSE Endocardial Ablation System. Forty (40) patients were enrolled between January and December of 2018. Thirty (30) patients were enrolled in Prague and ten (10) were enrolled in Bordeaux. All patients were discharged in good condition. One patient was treated for tamponade at the conclusion of the Index Procedure and the event was resolved. Three patients were re-hospitalized for atrial arrhythmia and all of these events were resolved. One patient experienced a prolonged index hospitalization due to an arteriovenous groin fistula which was resolved. At the conclusion of the index Procedure, all (100%) pulmonary veins (PVs) were isolated using the FARAPULSE Endocardial Ablation System. Thirty-five (35) patients have returned for the protocol-defined 3-month remapping procedure to assess durable PV isolation. In these patients, 70% of PVs remained isolated. All PVs in fourteen (14) patients remained isolated. These results support the safety and performance of the system.

1.3.2 Endocardial Ablation Studies – The PEFCAT Study

FARAPULSE, Inc. has also initiated a safety and feasibility study at Na Homolce Hospital in Prague, Czech Republic and Hopital Cardiologique du Haut-Leveque in

Pessac, France under the "PEFCAT" Protocol, CS0267. This study is being conducted using the FARAPULSE Endocardial Ablation System. Sixty (60) patients have been enrolled between October 2018 and June 2019. Fifty (50) patients were enrolled in Prague and ten (10) were enrolled in Bordeaux. All patients were discharged in good condition. One patient was treated for an air embolism during the index Procedure and the event was resolved. Three patients were re-hospitalized for atrial arrhythmia and all of these events were resolved. One patient was hospitalized for back pain and the event was resolved. One patient experienced a prolonged index hospitalization due to an arteriovenous groin fistula which was resolved. At the conclusion of the index Procedure, all pulmonary veins (PVs) in all patients were isolated using the FARAPULSE Endocardial Ablation System. Fourty-nine (49) patients have returned for the protocol-defined 75-day remapping procedure to assess durable PV isolation. In these patients, 96% of PVs remained isolated. All PVs in thirty-nine (39) patients undergoing reassessment remained isolated. These results support the safety and performance of the system.

1.4 Rationale for Conducting This Feasibility Study

Catheter ablation for PAF with a variety of energy sources and catheter configurations has been demonstrated to be a safe and effective procedure. The FARAPULSE Endocardial Multi Ablation System has undergone preclinical and clinical testing to demonstrate that it can isolate pulmonary veins quickly and with minimal complications, using a standard catheter-based endocardial procedure. Ongoing clinical follow-up demonstrates durable lesions at 75 day remapping procedures.

This study expands the use of the the FARAPULSE Endocardial Multi Ablation System to the treatment of patients with PersAF. The availability of both the FARAWAVE Ablation Catheter and the FARAFLEX Ablation Catheter allow the delivery of PEF ablation in the same locations as existing treatment such as RF ablation, and thus permit treatment of PersAF.

Potential Risks: Based on the growing experience with the similar FARAPULSE Endocardial Multi Ablation System, the risks associated with this small feasibility study are not expected to differ from those products that are approved and available on the market for catheter-based or surgical ablation procedures. In addition, verification and validation testing of the FARAPULSE Endocardial Multi Ablation System will ensure device safety and performance during the clinical investigation as well as compliance with the applicable parts of the Medical Device Directive 93/42/EEC. FARAPULSE will ensure through its Risk Management processes that the residual risks have been reduced to a level that is as low as possible.

Potential Benefits: A study of up to 40 patients for assessment in this protocol will have the following potential benefits:

- To provide treatment to subjects with PersAF using an investigational device which has demonstrated the ability to isolate pulmonary veins and reduce the subsequent occurrence of symptomatic atrial fibrillation in a small number of patients

- To generate additional data demonstrating that the endocardial creation of electrically isolating lesions via Pulsed Electric Field (PEF) catheter ablation applied using the FARAPULSE Endocardial Multi Ablation System is a safe and potentially effective treatment for drug-resistant, recurrent, symptomatic persistent atrial fibrillation (PersAF);
- To assess the feasibility and safety of the FARAFLEX Ablation Catheter for focal ablation in accordance with its proposed indication for use;
- To assess the protocol elements and design for subsequent use in an expanded multi-center European CE Mark Trial.

Please see **Section 4.0, Benefit Risk Assessment**, for additional details regarding the assessment of benefits and risks associated with this study.

2. Investigational Devices

2.1 Names of Investigational Devices

The FARAPULSE Endocardial Multi Ablation System is comprised of the following devices:

- FARAWAVE Endocardial Ablation Catheter
- FARAFLEX Endocardial Ablation Catheter
- FARASTAR Endocardial Generator System
- FARADRIVE Deflectable Sheath.

2.2 Intended Use

The FARAPULSE Endocardial Multi Ablation System is indicated for the treatment of drug refractory, recurrent, symptomatic persistent atrial fibrillation.

The FARAFLEX Endocardial Ablation Catheter is used as an adjunctive device in the endocardial treatment of persistent atrial fibrillation with the following intended uses:

- Gap ablation to complete electrical isolation of the pulmonary veins,
- Focal ablation of cardiac arrhythmias, and
- Creation of ablation line between the inferior vena cava and the tricuspid valve.

2.3 Classification

The FARAWAVE Endocardial Ablation Catheter and FARAFLEX Endocardial Ablation Catheter are classified as Class III medical devices. Per MDD 93/42/EEC Annex IX Rule 6 applies to the ablation catheters, which defines the catheters as surgically invasive devices intended for transient use (<60 min) that specifically controls, diagnoses, monitors or corrects a defect of the heart or of the central circulatory system through direct contact with these parts of the body.

The FARASTAR Endocardial Generator System is classified as a Class IIb medical device. Per MDD 93/42/EEC Annex IX Rule 9 applies to the generator system, which defines it as an active therapeutic device that is intended to administer or exchange energy to and from the human body in a potentially hazardous way, taking account of the nature, the density and the site of application of the energy.

The FARADRIVE Deflectable Sheath is classified as a Class III medical device. Per MDD 93/42/EEC Annex IX Rule 6 applies to the Deflectable Sheath System, which defines it as a surgically invasive device intended for transient use (<60 min) that specifically controls, diagnoses, monitors or corrects a defect of the heart or of the central circulatory system through direct contact with these parts of the body.

2.4 FARAPULSE Endocardial Multi Ablation System

The FARAPULSE Endocardial Multi Ablation System used in the proposed clinical investigation consists of the FARAWAVE Endocardial Ablation Catheter, the FARAFLEX Endocardial Ablation Catheter, the FARASTAR Endocardial Generator System, and the FARADRIVE Deflectable Sheath. These components, sub-components and model numbers are listed in **Table 1**.

Table 1. FARAPULSE Endocardial Multi Ablation System – Components

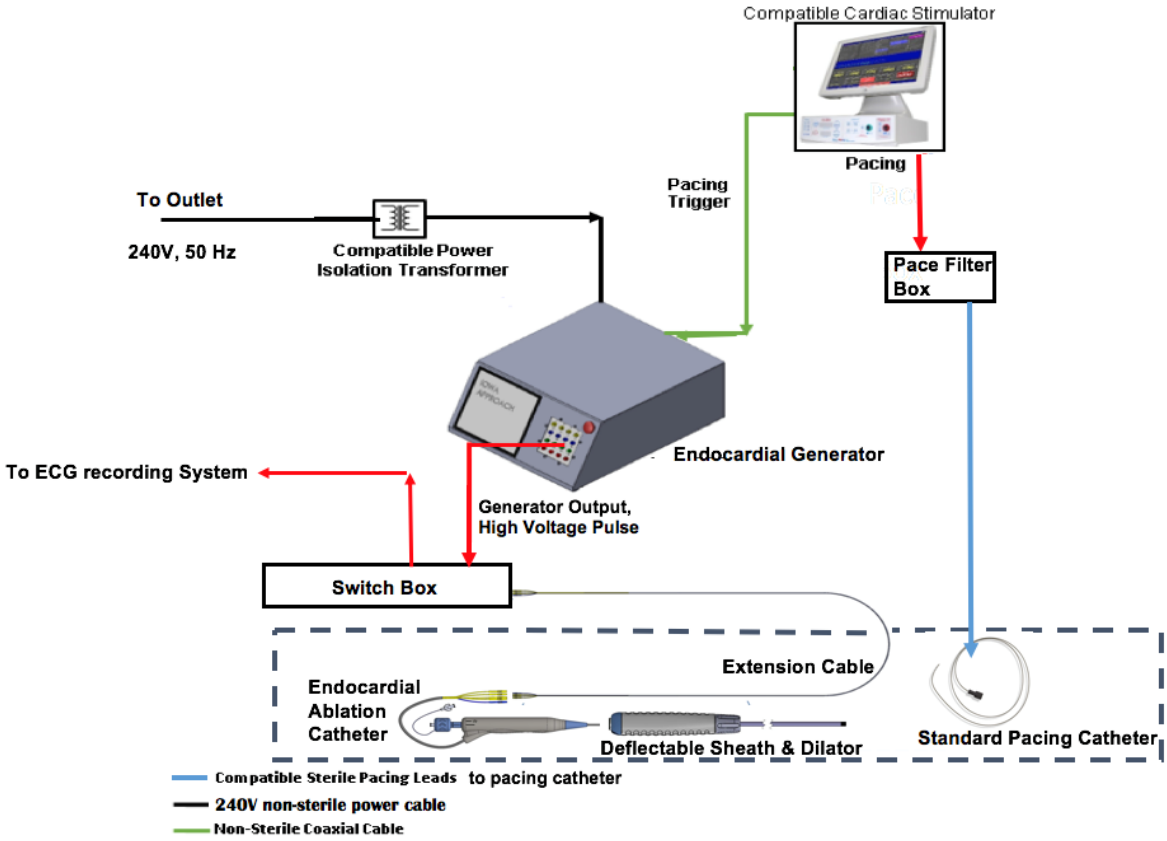
Component	Sub Components	Model Numbers
FARAWAVE Endocardial Ablation Catheter	1. Ablation Catheter (31 mm or 35 mm fully deployed diameter) 2. Extension Cable	40T401 (31 mm) and 40T404 (35 mm) 40T407 (extension cable)
FARAFLEX Endocardial Ablation Catheter (adjunctive device)	1. Ablation Catheter (17 mm fully deployed diameter) 2. Extension Cable	40T405 (catheter) 40T406 (extension cable)
FARASTAR Endocardial Generator System	1. Pulsed Electric Field Generator (PEFG) 2. Two Coaxial Cables 3. Pace Filter Box 4. Two Catheter Switch Boxes	60T401
FARADRIVE Deflectable Sheath (or commercially available CE Marked Deflectable Sheath System such as the CE Marked Oscor Destino™ Twist UniDirectional Deflectable Guiding Sheath)*	1. Sheath 2. Dilator	20T401

During the course of the investigation certain CE Marked medical devices may be used in conjunction with the FARAPULSE Endocardial Multi Ablation System. These are listed in **Table 2**.

Table 2. CE Marked Devices Utilized in Conjunction with FARAPULSE System

CE Marked Devices That May be Used in Conjunction with FARAPULSE Endocardial Multi Ablation System
*Oscor Destino™ Twist UniDirectional Deflectable Guiding Sheath
St. Jude BRK 98cm Transseptal Needle
MicroPace StimCor Cardiac Stimulator

A schematic of the FARAPULSE Endocardial Multi Ablation System is depicted in **Figure 1** following.



Note: Blue dotted box shows the sterile, single-use components of the system

Figure 1. FARAPULSE Endocardial Multi Ablation System Components

2.4.1 FARAWAVE Endocardial Ablation Catheter System

The FARAWAVE Endocardial Ablation Catheter System consists of two (2) components: Ablation Catheter and Extension Cable, which are used together. Both components are sterile and single use only.

The ablation catheter is offered in two different sizes: 31 mm (REF 40T401) and 35mm (REF 40T404) deployed diameters, to accommodate varying pulmonary vein anatomy. Selection of either catheter will be at the investigator's discretion.

The Ablation Catheter is a multi-electrode catheter that connects electrically to the Endocardial Generator System. It consists of a multi-electrode ablation catheter with electrodes arranged on splines. The Ablation Catheter consists of a distal section with five splines that deploy into a basket-shaped configuration or flower-shaped configuration with five petals, a shaft section, and a proximal handle with a manually operated deployment control (**Figure 2**), which depicts a fully deployed distal flower-shapedconfiguration.

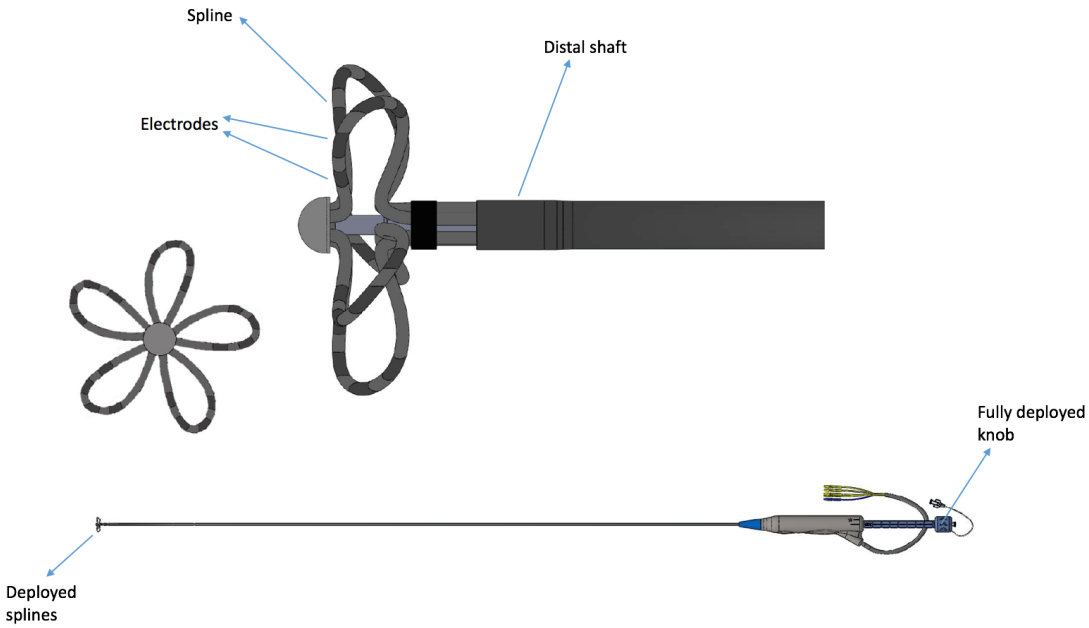


Figure 2. FARAWAVE Endocardial Ablation Catheter

Each spline has a single electrode that is separately wired to facilitate connection to a mapping or recording system (this is an optional feature offered to the user). The handle includes a flush port for saline infusion, a deployment control knob with a guidewire lumen hub that can be connected to a hemostasis valve, and a cable with connectors. The catheter connectors connect to an Extension cable (part of the Endocardial Ablation Catheter System) with numbered connectors on each of its ends. These connect to the multi-channel FARASTAR Endocardial Generator. The Pulsed Electric Field energy is delivered via the FARASTAR Endocardial Generator over the set of ablation catheter electrodes. The Extension Cable is a single-use sterile cable that provides additional cable length to connect to the FARASTAR Endocardial Generator.

Additional details are provided in the IFU LBL0195 for the specific use and procedural steps of the FARAWAVE Endocardial Ablation Catheter.

2.4.2 FARAFLEX Endocardial Ablation Catheter

The FARAFLEX Endocardial Ablation Catheter is a multi-electrode unidirectional, deflectable percutaneous catheter that connects to the FARASTAR Endocardial Generator and is designed to deliver PEF energy from the Endocardial Generator for cardiac tissue ablation. The FARAFLEX Endocardial Ablation Catheter is an adjunctive catheter designed to create smaller focal-type lesions for the following indications for use:

- Gap ablation to complete electrical isolation of the pulmonary veins,
- Focal ablation of cardiac arrhythmias, and
- Creation of ablation line between the inferior vena cava and the tricuspid valve.

The catheter consists of the following major sections: 1) distal section with electrodes arranged on four (4) splines, 2) catheter shaft, and 3) proximal handle with manually operated deflection and deployment controls, flush port, and connector. **Figure 3** depicts a deployed FARAFLEX Endocardial Ablation Catheter.

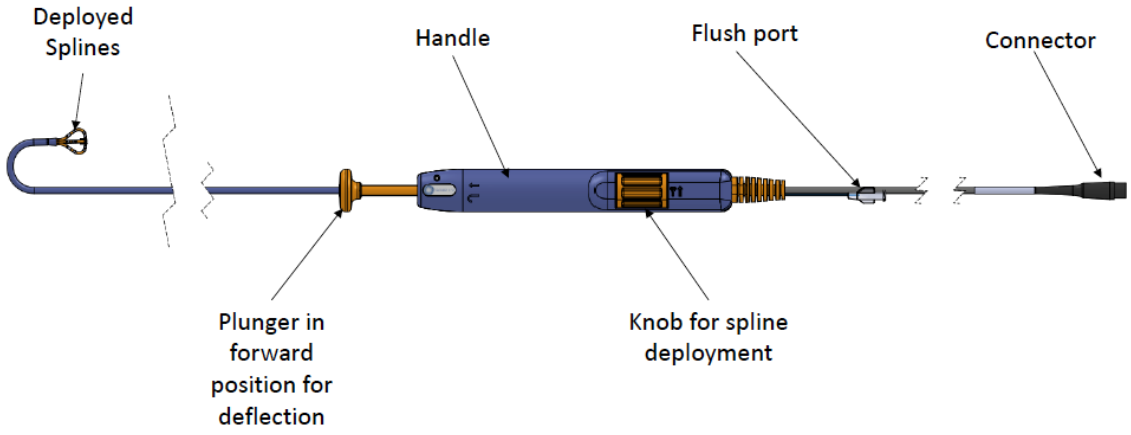


Figure 3. FARAFLEX Endocardial Ablation Catheter

The catheter can be deployed into basket-shaped configurations to accommodate various anatomical locations. The ablation catheter is visible under fluoroscopy due to the presence of marker bands at the distal tip and proximal end of the splines, as well as electrodes on each of four (4) splines.

2.4.3 FARASTAR Endocardial Generator System

The FARASTAR Endocardial Generator System consists of the following components – Pulsed Electric Field Generator (PEFG), BNC Coaxial Cable (2 units), Pace Filter Box (1-2 units), and Switch Box (2 units). The Endocardial Generator System is designed to deliver PEF energy to endocardial sites in the heart via the FARAWAVE and FARAFLEX Endocardial Ablation Catheters and other compatible devices (refer to IFU LBL0195 and IFU LBL0565 for the specific use and procedural steps of the Endocardial Ablation Catheters, respectively; LBL0193 for the FARADRIVE Deflectable Sheath and LBL0198 for the FARASTAR Endocardial Generator System).

The FARASTAR Endocardial Generator is a 16-channel output unit that generates a pulsed voltage waveform that can be delivered to the ablation catheter electrodes. The FARASTAR Generator, while capable of operating between 1400V and 2100V, currently allows ablation energy in discrete user-selectable voltage settings between 1400V and 2000V.

As an input, a compatible cardiac stimulator unit for cardiac pacing is applied to the cardiac chambers via pacing catheters and to the FARASTAR Endocardial Generator with a coaxial cable to synchronize the application of therapeutic PEF energy to the actively paced heart. The physician confirms proper synchronization by actuating a

button on the FARASTAR Endocardial Generator user interface. The BNC Coaxial Cable is used to connect the generator to a commercially available compatible cardiac stimulator/pacing device.

Details regarding the generator are provided in the FARASTAR Endocardial Generator System User Manual LBL0198.

2.4.4 FARADRIVE Deflectable Sheath

The FARAWAVE Endocardial Ablation Catheter and FARAFLEX Endocardial Ablation Catheter are used with the FARADRIVE Deflectable Sheath or a compatible CE Marked Deflectable Sheath System (13F) such as the CE Marked Oscor Destino™ Twist UniDirectional Deflectable Guiding Sheath.

The FARADRIVE Deflectable Sheath consists of two (2) primary components: Deflectable Sheath and Dilator, which are used together. Both components are sterile and single use only.

The FARADRIVE Deflectable Sheath is comprised of a distal deflectable section and a shaft section which connect to the handle. The handle includes a knob to control the deflection of the distal tip and a flush port for infusion of saline or contrast. The Dilator is intended for insertion through the sheath lumen and includes a shaped tip for dilation for vascular or chamber access (**Figure 4**).

Figure 4. FARADRIVE Deflectable Sheath and Dilator

2.5 Device Accountability

The FARAPULSE Endocardial Multi Ablation System will be stored in a secure location and access will be controlled. Records will be maintained to document the physical location of inventory from shipment and removal from Sponsor or Contract Manufacture facility through use and / or return or disposal.

The site will be responsible for maintaining a Device Accountability Log provided by the Sponsor or its designated representative. At a minimum the following will be recorded: Date of receipt, FARAPULSE Endocardial Multi Ablation System

components identification number (Generator, Ablation Catheter and Deflectable Sheath lot and / or serial number), expiration date, date of use, subject unique identification code and date of disposal or return of the device.

If there is a product Device Deficiency / Malfunction or other need to return the system or system components to the Sponsor or Contract Manufacture, the Sponsor or designee should be contacted for safe product disposal and/ or return details. Appropriate CRF will be completed in the event of a Device Deficiency / Malfunction.

The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the study. The Investigator shall document on the Case Report Forms (CRFs) the lot numbers and / or serial numbers of the devices used during each case.

2.6 Return of Devices

All unused investigational devices will be returned to the Study Sponsor or designee upon completion of the clinical study. Any investigational device that does not meet performance specifications will also be returned to the Study Sponsor or designee for analysis per company procedures. The Investigator or his/ her designated representative is responsible for device accountability and disposition of all used and unused devices. The Study Sponsor or its designated representative will conduct device reconciliation at the completion of subject enrollment or at the conclusion of the study.

3. Study Design

3.1 Study Objective

The objective of this safety and feasibility study is to assess whether the endocardial creation of electrically nonconductive lesions via PEF catheter ablation applied using the FARAPULSE Endocardial Multi Ablation System is a feasible and safe treatment for PersAF and associated AFL.

3.2 Study Overview

This is a prospective, multi-center, unblinded single arm safety and feasibility study. Subjects will undergo percutaneous PEF ablation for pulmonary vein isolation and at the clinical discretion of the investigator receive PEF ablation of additional arrhythmogenic locations. Subjects will be followed at 30 days, 75 days, 6 months and 12 months for adverse events, recurrence of arrhythmia after a 90-day Blanking Period and other relevant outcome measures.

3.3 Subject Confidentiality

Enrolled subjects will be assigned a unique, pseudo-anonymous identifier that will be used to maintain confidentiality of each subject's medical information. Subject names and other protected health information will not be captured on the CRFs. In addition, all patient identifiers except the unique pseudo-anonymous identifier should be redacted from any images or other data submitted from the participating site to the Sponsor or the Sponsor's designated reviewers for analysis. All information concerning subjects or their participation in this study will be considered confidential. Only the authorized Sponsor, designated representative personnel, designated consultants and regulatory agencies will have access to these confidential files.

3.4 Written Informed Consent

All subjects must provide written Informed Consent using the EC-approved ICF before undergoing any study related procedures.

Routine clinical evaluations that would be performed as part of the normal clinical care of patients may be performed prior to such consent and used as part of the screening assessment. If the subject is subsequently consented and enrolled in the study, the results of such evaluations may be used as study data.

Subjects cannot be asked to sign the ICF until the study has been fully approved by the institution's EC and by the CA, if applicable, and the Sponsor or their CRO representative has received and reviewed the EC-approved ICF. Subjects who meet the general entry criteria will be asked to sign an ICF as approved by the relevant regulatory authorities before any study-specific tests or procedures are performed.

The Investigator or a designated member of his / her staff should approach the subject to obtain written informed consent. As far as possible, non-technical language shall be used that is understandable to the subject. The background of the proposed study and the benefits and risks of the procedures and study should be explained. The subject should be provided with ample time to read the ICF and discuss it with their family and physician. The subject shall be informed that his / her participation in the clinical

investigation is confidential. The ICF must be read and understood by the subject and the subject's questions answered. The ICF must be signed and dated by both the subject and Investigator conducting informed consent prior to subject enrollment and before the subject undergoes any study-related procedures. All subjects are to receive copies of their signed and dated ICF. A copy of the approved ICF along with a copy of each patient's signed ICF will be maintained by the Investigator in a designated clinical study administrative file. Subjects may not be consented after receiving any medication that might alter their ability to comprehend the consent form (e.g. sedatives, narcotics, etc.). Study personnel should explain that even if a subject agrees to participate in the study and signs the ICF, the subject may not be eligible to participate if he / she fails to meet the screening criteria.

Written informed consent must be obtained prior to performing any protocol driven tests or any procedures that are not standard of care for a percutaneous ablation procedure that the subject is scheduled to undergo.

Once written consent has been obtained, the subject will be entered on a Screening Log, which will be maintained at each site. All subjects who provide written informed consent will be entered on the screening log regardless of whether or not they are enrolled in the study.

3.5 Study Entry Criteria

3.5.1 Inclusion Criteria

Study subjects are required to meet all the following inclusion criteria to participate in this study:

1. Patients with documented drug-resistant symptomatic persistent AF meeting all three of the following criteria:
   a. Patient is refractory or intolerant to at least one Class I/III antiarrhythmic agent.
   b. ECG-documented first episode of persistent AF, lasting longer than 7 days but not longer than 365 days
   c. Holter within 90 days prior to the Enrollment Date demonstrating 24 hours of continuous AF
2. Patients who are ≥ 18 and ≤ 75 years of age on the day of enrollment.
3. Patient participation requirements:
   a. Lives locally.
   b. Is willing and capable of providing Informed Consent to undergo study procedures.
   c. Is willing to participate in all examinations and follow-up visits and tests associated with this clinical study.

3.5.2 Exclusion Criteria

Subjects will be excluded from participating in this study if they meet any one of the following exclusion criteria:

1. Atrial fibrillation that is any of the following:
   a. Paroxysmal (longest AF episode < 7days)
   b. Longstanding (has persisted > 12 months or that does not respond to cardioversion if < 12 months)
   c. Secondary to electrolyte imbalance, thyroid disease, alcohol abuse or other reversible / non-cardiac causes
2. Left atrial anteroposterior diameter ≥ 5.5 cm as documented by transthoracic echocardiography (TTE) or computed tomography (CT)
3. Any of the following cardiac procedures, implants or conditions:
   a. Clinically significant arrhythmias other than AF, AFL or AT
   b. Hemodynamically significant valvular disease
   c. Prosthetic heart valve
   d. NYHA Class III or IV CHF
   e. Previous endocardial or epicardial ablation or surgery for AF
   f. Atrial or ventricular septal defect closure
   g. Atrial myxoma
   h. Left atrial appendage device or occlusion
   i. Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices
   j. Significant or symptomatic hypotension
   k. Bradycardia or chronotropic incompetence
   l. History of pericarditis
   m. History of rheumatic fever
   n. History of congenital heart disease with any residual anatomic or conduction abnormality
4. Any of the following within 3 months prior to enrollment:
   a. Myocardial infarction
   b. Unstable angina
   c. Percutaneous coronary intervention
   d. Heart surgery (e.g. coronary artery bypass grafting, ventriculotomy, atriotomy)
   e. Heart failure hospitalization
   f. Stroke or TIA
   g. Clinically significant bleeding
   h. Pericarditis or pericardial effusion
   i. Left atrial thrombus
5. History of blood clotting or bleeding abnormalities.
6. Contraindication to, or unwillingness to use, systemic anticoagulation.
7. Contraindications to CT or MRI.
8. Sensitivity to contrast media not controlled by premedication.
9. Women of childbearing potential who are pregnant, lactating or not using birth control.
10. Medical conditions that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or confound data or its interpretation, including but not limited to:

a. Body mass index (BMI) > 40
b. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
c. Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or significant dyspnea
d. Renal insufficiency with an estimated creatinine clearance < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant
e. Active malignancy or history of treated cancer within 24 months of enrollment
f. Clinically significant gastrointestinal problems involving the esophagus, stomach and/or untreated acid reflux
g. Clinically significant infection
h. Predicted life expectancy less than one year

11. Clinically significant psychological condition that in the investigator's opinion would prohibit the subject's ability to meet the protocol requirements.
12. Current or anticipated enrollment in any other clinical study.
13. Employment by FARAPULSE or the same hospital department or office of any investigator, or a family member of any of the preceding groups.
14. Use of amiodarone after day of index ablation procedure. Patients will cease use of amiodarone on or before the date of the index ablation procedure.

3.6 Enrollment

Subjects that meet all of the eligibility criteria and are deemed suitable by the investigator will be invited to participate in the study.

Subjects will be considered enrolled at the time of signing the ICF.

Each subject will be assigned a unique study identification code to protect each subject's confidential health information. The unique study identification code will not include date of birth or subject's first and last initials and will be used to link study data and other study information to the subject in lieu of the subject name. The Subject Name Log will be used to link the unique study identity code to the subject and will be maintained at the site. This log will remain confidential and will not be provided to the Sponsor, but only used for reference when monitoring at the study site.

3.7 Sample Size

Up to 40 subjects in total will be enrolled at up to four sites in this clinical safety and feasibility study. Approved sites will enroll at least 5 and not more than 20 subjects.

3.8 Investigational Sites

The clinical study will be conducted at up to four investigational sites.

3.9 Duration of Subject Participation

Subjects will be followed at 30 days, 75 days, 6 months and 12 months with a 90-day Blanking Period for recurrent atrial fibrillation, atrial flutter or atrial tachycardia following the Index Procedure.

Reablation with the study device(s) during the Blanking Period is permitted but does not extend either the Blanking Period or the total follow-up interval.

The enrollment period is estimated to take 9 months and subjects will be followed for up to 12 months for a total duration of approximately 21 months.

3.10 Subject Completion or Withdrawal

3.10.1 Study Completion

Once the subject has completed the final 12 month follow-up visit they are to be exited from the study.

3.10.2 Voluntary Withdrawal

Subjects may voluntarily withdraw from the study at any time for any reason.

3.10.3 Investigator Initiated withdrawal

The investigator may withdraw the subject due to any of the following situations:

- adverse event (AE); or
- study investigator may withdraw a patient from the study without the patient's consent if the investigator has a concern for the patient's rights, safety or welfare

3.10.4 Documentation

At the time of study withdrawal or completion for any reason, the study exit CRF will be completed, including the reason for exit.

3.10.5 Continuing Medical Care

Subjects leaving the study at any time will continue to receive appropriate medical care without prejudice.

3.10.6 Lost to Follow-Up

If the investigator has attempted to contact a subject at least three times within 60 days and received no response, the subject may be considered lost to follow-up. The investigator will document that a minimum of three attempts were made to contact the subject, including sending a certified letter if current address is known, prior to exiting the subject from the study.

At the time of confirmed lost to follow-up status, the study exit CRF will be completed.

3.11 Procedures

3.11.1 Index Procedure

The investigator will confirm that the following have been achieved:

- For women of childbearing potential – a negative pregnancy test
- Baseline NIHSS score
- The patient is not on amiodarone

FARAPULSE Endocardial Ablation procedure patients will undergo anesthesia according to institutional protocol. They will then be prepared in conventional sterile fashion for a cardiac catheterization procedure. Femoral vein access will be obtained via Seldinger technique. Transseptal access to the left atrium will then be obtained using either a FARADRIVE Deflectable sheath or a commercially approved sheath and Brockenbrough needle. The transseptal sheath will then be withdrawn, leaving guidewire access to the left atrium. The FARADRIVE Deflectable Sheath, or a commercial equivalent as described above in **Table 2,** will then be prepared and advanced via guidewire to the left atrium. Commercially approved multielectrode pacing catheters will then be placed via conventional technique at the investigator's discretion. A baseline electrophysiological assessment of pulmonary vein connection to the left atrium will be made and documented via FARAWAVE or a commercially approved diagnostic catheter placed in each addressable pulmonary vein. A baseline 3D electroanatomical map may also be made at the investigator's discretion. The diagnostic catheter will then be removed from the FARADRIVE Deflectable Sheath or commercial equivalent.

The FARAWAVE Ablation Catheter will then be prepared and advanced over the guidewire to the left atrium through the sheath. The guidewire will be advanced into a target pulmonary vein, the catheter splines will be deployed to suit target anatomy by retracting the deployment knob, and the deployed catheter will be advanced to the ostium of the target pulmonary vein. At the investigator's discretion, contrast venography may be performed to verify placement of the catheter at the ostium. Cardiac pacing capture from the external cardiac stimulator will be obtained via connection to a diagnostic catheter. Once pacing capture is confirmed, ablation will be performed. Ablation dose will be selected at the investigator's discretion in accordance with LBL0198, FARASTAR Generator User Manual.

Ablation with the FARAWAVE Ablation Catheter may be repeated at the same site or at another target site at the physician's discretion using deployment configurations to suit target anatomy. Each addressable pulmonary vein will be ablated in turn beginning with placement of the guidewire, deployment of the ablation catheter, confirmation of pacing capture, and ablation. The effect of the ablation(s) may be checked post-procedure by pacing maneuvers, ECG recordings, 3D electroanatomic mapping, or by using the mapping electrodes on the ablation catheter splines. Ablation using the FARAFLEX Ablation Catheter may be performed to close gaps in electrical isolation of pulmonary veins, focally ablate cardiac arrhythmias, or create a line of ablation at the cavo-tricuspid isthmus (CTI).

For a detailed description of procedure workflow refer to LBL0193 (FARADRIVE Deflectable Sheath), LBL0195 (FARAWAVE Endocardial AblationCatheter), LBL0565 (FARAFLEX Endocardial Ablation Catheter and LBL0198 (FARASTAR Endocardial Generator System).

3.11.2 75-Day Remap Procedure

The 75-Day Remap Procedure will follow the steps contained in **Section 3.11.1, Index Procedure**, as determined by investigator discretion to achieve protocol-required mapping and any required reablation.

3.11.3 Blanking Period

The Blanking Period consists of Day 0 (the date of Index Procedure) through and including Day 90.

During the Blanking Period, any recurrence of AF will be documented; however, recurrences of AF, AFL or AT during this time will not be considered Therapeutic Failures.

Subjects may undergo one repeat ablation during the Blanking Period without creating a Therapeutic Failure, following the procedure detailed in the preceding sections. This may occur during the Remap Procedure or at another procedure as clinically indicated.

If a second repeat ablation procedure is performed during this time, or any nonstudy device is used for cardiac ablation, the subjects will be considered a Therapeutic Failure but will remain in the study.

Towards the end of the Blanking Period, any AFD treatment will be discontinued unless the Investigator deems the withdrawal of AFD treatment not to be in the best interests of the patient.

3.11.4 Arrhythmia Core Lab

An Arrhythmia Core Lab will oversee the provision, collection and analysis of data from the Event Monitors and Holter Monitors specified in this protocol.

- An Event Monitor will be provided at the 75-Day Remap to be used through the remainder of the 12-month follow-up interval for weekly scheduled and ad hoc symptomatic monitoring. Investigational sites will be provided with the Event Monitor and instructions for its use by the Arrhythmia Core Lab. The investigational sites will then provide the device and instructions for use to the subject. The Event Monitor will be returned to the Arrhythmia Core Lab at the time of the subject's exit from the study. ECG data from the Event Monitor will be analyzed by the Arrhythmia Core Lab.
- A 24-hour continuous ECG monitor will be provided at the 6 and 12-Month Visits. Investigational sites will be provided with the continuous ECG monitor device and instructions for its use by the Arrhythmia Core Lab. The investigational sites will then provide the device and instructions for use to the subject. The device will be worn by the subject for a single 24-hour period and

then returned to the Core Lab with shipping materials provided by the core lab. ECG data from this monitor will be analyzed by the Core Lab.

3.12 Schedule of Events and Assessments

Subjects will complete the following visits and assessments as indicated below and as summarized in **Section 3.12 Table 3 Summary of Study Assessments**.

3.12.1 Baseline

The following baseline data will be collected:

- Medical history
- AFD and anticoagulation medication history
- Pregnancy test (all women of child-bearing potential)
- 12-lead ECG
- Cardiac CT or MRI adequate to characterize left atrial and pulmonary vein dimensions
- TEE or other imaging modality for exclusion of left atrial thrombus
- NYHA Classification
- NIHSS score
- CHA_2DS_2-VASc score

3.12.2 Index Procedure

The Index Procedure will be performed according to **Section 3.11.1, Index Procedure**. The following procedural data will be collected:

- Pregnancy test (all women of childbearing potential if baseline pregnancy test obtained more than 14 days prior to procedure)
- Post-ablation 3D electroanatomical maps
- Post-ablation fluoroscopic examination of diaphragm motion to assess phrenic nerve response
- Adverse Events
- Procedural times
- Lesion set data
- Device deficiencies and malfunctions

3.12.3 Pre-Discharge

Prior to hospital discharge the following data will be collected:

- Adverse Events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Cardiac rhythm as determined by a 12-lead ECG
- Occurrence, date, indication and outcome of any cardioversion(s)
- At the investigator's discretion: a post-procedural mediastinal gadolinium-enhanced MRI
- Stroke/TIA assessments

- NIHSS score
- A neurologic examination will be performed and recorded if:
  - If the NIHSS score has increased by 2 or more points
  - If there is a clinical suspicion of stroke or TIA

3.12.4 30-Day Visit

Discharged subjects will return for an office visit 30 days (± 7 days) post-ablation treatment. (Any subject who continues to be hospitalized 30 days post-ablation will have their 30-Day Visit assessment performed in-hospital). The following data will be collected at the 30-Day Visit:

- Adverse Events
- Symptoms of recurrent arrhythmia
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit
- Cardioversions, ablations or hospital admissions since last visit
- Heart failure status as assessed by NYHA classification at the time of visit

3.12.5 75-Day Visit and Remapping Procedure

Patients undergoing protocol-specified remapping:

Subjects will undergo the protocol-stipulated remapping procedure at 75 ± 15 days post-Index Procedure as defined in **Section 3.11.2, 75-Day Remap Procedure**.

- A 3D electroanatomical remapping procedure will be performed to assess electrical isolation of the pulmonary veins. Any electrical gaps may be closed at the investigator's discretion using study devices, or if necessary, a commercially approved ablation device (which constitutes a Therapeutic Failure).
- For patients who received extra-PV ablation at index, including those receiving ablation of the CTI, the persistence of nonconductivity in targeted tissue will be evaluated with either pacing maneuvers or electroanatomical mapping.

Procedure-specific data will be collected as follows:

- Procedural times
- Lesion set data
- Device deficiencies and malfunctions

All subjects whether undergoing remapping or not:

- Event Monitor: An Event Monitor and training will be provided to the subject, to be used for weekly scheduled and ad hoc symptomatic monitoring through the remainder of study follow-up. (**See Section 3.11.4, Arrhythmia Core Lab**). If necessary patients will be provided with an Event Monitor by mail, telephonic training and successful transmission of a monitoring record.
- AFD Management: For patients who do not require reablation during the 75-Day remap visit AFD may be stopped at the investigator's discretion.

The following data will be collected from all subjects at 75 ± 15 days:

- Adverse Events
- Symptoms of recurrent arrhythmia
- Fluoroscopic examination of diaphragm motion is required if:
  - Patient underwent remapping to assess phrenic nerve response
  - The patient declined a remap procedure but the post Index Procedure fluoroscopic examination indicated diminished phrenic nerve response
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Pregnancy test (all women of child-bearing potential) prior to remap
- Cardiac rhythm as determined by a 12-lead ECG
- Cardiac CT or MRI scan to assess the patency of the pulmonary veins
- Cardioversions, ablations or hospital admissions since last visit
- Heart failure status as assessed by NYHA classification at the time of visit

3.12.6 6-Month Visit

Subjects will return for an office visit 6 months (180 days ± 30 days) following the Index Procedure. The following data will be collected at the 6-Month Visit:

- Adverse Events
- Symptoms of recurrent arrhythmia
- If either the post-Index Procedure or post-75-Day Remap Procedure fluoroscopies indicated diminished phrenic nerve response, and resolution has not been previously demonstrated, a repeat fluoroscopic examination. Females of childbearing potential undergoing this examination will also receive a pregnancy test prior.
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit
- Arrythmia assessment (See **Section 3.11.4, Arrhythmia Core Lab**).
  - A 24-hour continuous ECG monitor and training will be provided to the subject
  - Event Monitor compliance will be reviewed for weekly scheduled and ad hoc symptomatic monitoring and retraining of the subject provided as needed
- Cardioversions, ablations or hospital admissions since last visit
- Heart failure status as assessed by NYHA classification at the time of visit

3.12.7 12-Month Visit

Subjects will return for an office visit 12 months (365 days ± 30 days) following the Index Procedure. At a minimum, the following data will be collected at the 12-Month Visit:

- Adverse Events

- Symptoms of recurrent arrhythmia
- If either the post-Index Procedure or post-75-Day Remap Procedure fluoroscopies indicated diminished phrenic nerve response, and resolution has not been previously demonstrated, a repeat fluoroscopic examination. Females of childbearing potential undergoing this examination will also receive a pregnancy test prior.
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit
- Arrythmia assessment (See **Section 3.11.4, Arrhythmia Core Lab**).
  - A 24-hour continuous ECG monitor will be provided to the subject.
  - Instructions for returning the Event Monitor will be provided
- Cardioversions, ablations or hospital admissions since last visit
- Heart failure status as assessed by NYHA classification at the time of visit

3.12.8 Unscheduled Visits

Any unscheduled follow-up visits that occur throughout the study, other than routine follow-up visits per the institution's or investigator's normal standard of care, shall be documented. At the minimum, the following data will be collected:

- Adverse Events
- Symptoms of recurrent arrhythmia
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit
- Event Monitor compliance will be reviewed for weekly scheduled and ad hoc symptomatic monitoring and retraining of the subject provided as needed.
- Cardioversions, ablations or hospital admissions since last visit
- Heart failure status as assessed by NYHA classification at the time of visit

3.13 Schedule of Study Assessments

Table 3. Summary of Study Assessments

Assessment	Baseline	Procedure	Pre-Discharge	30-Days Post-Procedure (± 7 days)	75-Days (± 15 days)	6-Month (180 ± 30 days)	12-Month (365 ± 30 days)	Unscheduled
Medical History, CHA_2DS_2-VASc	X							
AFD and Anticoagulant Medications	X		X	X	X	X	X	X
Symptoms of recurrent arrhythmia				X	X	X	X	X
History of cardioversions, ablations, hospital admissions since last visit			X	X	X	X	X	X
Pregnancy test (for females of childbearing potential)	X	X			X	X[4]	X[4]	
12-lead ECG	X		X	X	X	X	X	X
24-Hour Continuous ECG Monitor (e.g., Holter)						X	X	
Cardiac CT/MRI for LA and PV dimensions	X				X			
Mediastinal MRI			X[1]					
TEE or other imaging modality (to exclude left atrial thrombus)	X							
Electroanatomical Mapping		X			X			
Event Monitor readiness/compliance					X	X	X	X
NIHSS	X		X					
Neurologic exam			X[2]					
NYHA Classification	X		X	X	X	X	X	X
Fluoroscopic Examination of Diaphragm		X			X if remapped, X[3] if not	X[3]	X[3]	
Adverse Events		X	X	X	X	X	X	X

[1] At investigator's discretion
[2] If NIHSS score has increased by 2 or more points or if clinical suspicion of stroke/TIA
[3] If the Index Procedure or Remap Procedure study indicated decreased phrenic nerve function and resolution has not yet been demonstrated.
[4] As required for females of childbearing potential undergoing fluoroscopic examination of the diaphragm

4. Benefit Risk Assessment

The Sponsor has conducted an analysis of the benefits and risks of the FARAPULSE Endocardial Multi Ablation System and ablation procedure as described below. The conclusion of this review is that the subject investigation is justified because the overall potential benefit to the population outweighs the risks.

4.1 Potential Adverse Events

The following anticipated adverse events have been identified as possible complications of percutaneous atrial fibrillation ablation procedures in general as well as with the FARAPULSE Endocardial Multi Ablation System:

- Access site complications (e.g., hematoma, pseudo-aneurysm, laceration, bleeding) potentially requiring surgical intervention
- Air embolism
- Allergic reaction or fever resulting from contact with catheters
- Anemia
- Arrhythmia, potentially requiring cardioversion, defibrillation, or rhythm management device
- Arteriovenous fistulae
- Back pain
- Bed sores
- Bleeding, hematoma, hemorrhage or aneurysm at vascular access sites
- Blood pressure changes including hypotension or hypertension
- Coronary artery or vein injury
- Cardiac tamponade or perforation
- Cardiac arrest or cardiac failure
- Catheter entrapment
- Cardiogenic shock
- Conduction system injury resulting in sinus arrest or heart block, either transient or permanent, potentially requiring pacemaker insertion
- Congestive heart failure
- Death
- Drug allergic reaction or side effects (e.g., from contrast, steroids, analgesics, anesthetics, anticoagulants, sedatives, etc.)
- Embolism due to presence of thrombus or introduction of air
- Esophageal injury, ulcer or fistula
- Hemorrhage
- Hemodynamic compromise
- Hemopericardium
- Hemoperitoneum
- Hemothorax
- Local infection, systemic infection, and/or sepsis
- Muscle contractions due to electric stimulation
- Myocardial infarction / transient ischemia

- Nerve damage
- Organ failure
- Pain
- Perforation (e.g., of diaphragm, liver, lung, and/or vessels).
- Pericardial irritation
- Pericardial effusion
- Pericarditis
- Peritonitis
- Phrenic nerve injury with paralysis of the diaphragm and breathing impairment
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Pneumothorax
- Pulmonary vein injury or stenosis
- Risk of cancer or birth defect/harm to fetus from x-ray exposure
- Skin burns/irritation from x-ray exposure
- Stroke/transient ischemic attack
- Surgical procedure to remove retained catheter
- Thrombosis
- Vessel damage, dissection, or occlusion.

4.2 Potential Risks

As detailed in **Section 1.4, Summary of FARAPULSE Clinical Studies,** the risk profile associated with the FARAPULSE Endocardial Multi Ablation System and the ablation procedure is expected to be consistent with similar devices currently in clinical use for percutaneous cardiac ablation for treatment of persistent atrial fibrillation.

The FARAPULSE Endocardial Multi Ablation System is a Pulsed Electric Field (PEF) ablation system that produces continuous transmural cardiac lesions to treat atrial fibrillation using an ablation procedure that is similar to other commercially available percutaneous ablation catheters. More specifically:

- The device system is used during percutaneous endocardial ablation procedures like other commercially approved catheter systems.
- The device system is composed of similar biocompatible materials.
- The device system is a non-thermal ablation technology with targeted cardiac tissue specific mechanism of ablation.
- The device uses the standard percutaneous techniques for ablation procedures.
- The device utilizes a standard irreversible electroporation generator to deliver energy in the form of ablation dose.

A fundamental difference between the FARAPULSE Endocardial Multi Ablation System and other commercially approved atrial fibrillation ablation systems is that the Pulsed Electric Field or irreversible electroporation energy is delivered through

electrodes embedded in the endocardial ablation catheter for delivery of such energy in the pulmonary veins.

As such, the potential risks are roughly equivalent to those associated with commercially released systems being used for percutaneous cardiac ablation procedures. Currently, the complication rates for commercially available catheters are low and have declined as physicians have continued to learn more about cardiac ablation techniques. Furthermore, FARAPULSE, Inc. has conducted bench and in-vivo testing to ensure safe use of the device during clinical investigation and is in compliance with the applicable requirements of the Medical Device Directive 93/42/EEC.

4.3 Potential Benefits

There are no *guaranteed* benefits from participation in this study. Information gained from the conduct of this study may also be of benefit to other persons with the same medical condition.

A study of up to 40 patients for assessment in this protocol will have the following potential benefits:

- To provide treatment to subjects with PersAF using an investigational device which has demonstrated the ability to isolate pulmonary veins and reduce the subsequent occurrence of symptomatic atrial fibrillation in a small number of patients treated for PAF (see **Section 1.4, Summary of FARAPULSE Clinical Studies**);
- To generate additional data demonstrating that the endocardial creation of electrically isolating lesions via Pulsed Electric Field (PEF) catheter ablation applied using the FARAPULSE Endocardial Multi Ablation System is a safe and potentially effective treatment for drug-resistant, recurrent, symptomatic persistent atrial fibrillation (PersAF);
- To assess the feasibility and safety of the FARAFLEX Ablation Catheter for focal ablation in accordance with its proposed indication for use;
- To assess the protocol elements and design for subsequent use in an expanded multi-center European CE Mark Trial.

5. Statistical Analysis and Reporting

A Statistical Analysis Plan (SAP) will be prepared that governs the collection, analysis and reporting of the data from this investigation. This section summarizes the essential elements of that plan.

5.1 General Statistical Considerations

All statistical analyses will be performed using validated statistical software. Continuous variables will be summarized using standard quantitative statistics: number of available observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be specified.

Categorical variables will be summarized using classical frequency statistics: number of available observations and percentages by categories. Percentages will be calculated on the number of available observations. The number of missing observations will also be specified.

When applicable, bilateral asymptotic or exact confidence intervals for binomial distributions will be calculated at the 95% level.

A full data listing will be prepared. Data will be pooled from all study sites.

All related and resulting reports, documents and data will be produced and maintained in such a way as to ensure their control and the protection of subject privacy as far as is reasonably practicable. Data files and analytic reports will be archived according to requisite regulatory standards.

5.2 Control of Systematic Error and Bias

Subjects are not randomized in this single arm study and therefore masking is not achievable. Error and bias are being controlled by several means, including a comprehensive set of study procedures as defined in the protocol to ensure consistent management and outcome measure assessment. Follow-up Holter monitoring and event monitoring data, and all MRI/CT dimensions of PVs, will be assessed objectively by third parties according to standard clinical protocols. Primary effectiveness and safety outcomes will be reviewed by an independent Clinical Events – Data Monitoring Committee (CEDMC). A complete Study Report will allow scientific and clinical reviewers to independently assess potential error and bias.

Study outcomes will be reviewed and adjudicated by an independent Clinical Events and Data Monitoring Committee (CEDMC) more fully described in **Section 9.10, Clinical Events and Data Monitoring Committee.**

5.3 Sample Size Justification

This investigation is the next phase of ongoing feasibility studies to allow the controlled introduction of a new cardiac ablation catheter (FARAFLEX Endocardial Ablation Catheter). This is a feasibility study with no formal hypothesis testing and therefore no required sample size. Study results will be

presented using descriptive statistics. Results from this study will be used to inform and design additional clinical studies.

Forty (40) subjects at up to four sites will allow the assessment of the modified devices and the initial experience and training of investigators and study staff at a new investigational site.

5.4 Subject Disposition

The disposition of all subjects enrolled in the study will be described in tables and diagrams, including numbers screened, treated and assessed at each scheduled follow-up interval. Subjects who do not complete the study will be enumerated and the reason(s) for their discontinuation will be described.

5.5 Imputation for Missing Data

Imputations for missing data in (e.g., withdrawn subjects, loss to follow-up, missing data) will not be performed. Analyses will be performed with all available data only.

5.6 Populations for Analysis

Enrolled Population: all subjects who provided their informed consent.

Safety Subjects/Intent to Treat Subjects: all enrolled subjects except those who terminate their participation prior to the beginning of the Index Procedure.

Per Protocol Subjects: Intent-to-treat subjects for whom the Index Procedure is finished without interfering investigational device deficiency or malfunction.

Reasons for exclusion from the populations will be given, and a summary of adverse events for these subjects, if any, will be provided.

5.7 Final Clinical Report

A final clinical report including these analyses will be prepared at the conclusion of the study or at such time as the study may be prematurely terminated. Copies of the final report will be provided to the investigator and their EC and to the CA as applicable.

6. Outcome Measures

6.1 Primary Safety Endpoint

The primary safety endpoint for this study is the Composite Safety Endpoint (CSE) defined as the incidence of the following early-onset and late-onset serious adverse events (SAEs) which are device- or procedure-related, as adjudicated by the CEDMC and defined below in **Table 4. Composite Safety Endpoint Definitions**.

Early onset (within 30 days of an Index or Remap Procedure)

- Death
- Myocardial infarction (MI)
- Persistent diaphragmatic paralysis
- Stroke or transient ischemic attack (TIA)
- Peripheral or organ thromboembolism
- Pericarditis
- Cardiac tamponade / perforation
- Vascular access complications requiring intervention
- Heart block

Late onset (any time during follow-up through 12 months)

- Pulmonary vein (PV) stenosis (> 70% diameter reduction from baseline)
- Atrio-esophageal fistula

Table 4. Composite Safety Endpoint Definitions

Adverse Event	Description/Criteria
Death	Death
Myocardial infarction (MI)	Myocardial infarction will be demonstrated by any one of the following: 1) detection of ECG changes indicative of new ischemia (new ST-T wave changes or new LBB) that persist for more than 1 hour. 2) development of new pathological Q waves on an ECG 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Persistent diaphragmatic paralysis	Diaphragmatic paralysis: Change from baseline diaphragmatic function as demonstrated radiographically by elevation of the diaphragm above the normal range but not due to a pulmonary process such as atelectasis. Permanent: not resolved by completion of study follow-up
Stroke or transient ischemic attack (TIA)	Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause (ischemia or hemorrhage) in which symptoms last more than 24 hours, or if symptoms last less than 24 hours, a brain imaging study demonstrates infarction. Transient ischemic attack is a new focal neurological deficit with rapid symptom resolution always within 24 hours.

Adverse Event	Description/Criteria
Peripheral or organ thromboembolism	Formation in a blood vessel of a clot (thrombus) that results from the breaking loose of all or part of an existing thrombus, which is then carried by the blood to lodge in/occlude a more distal vascular site.
Pericarditis	Inflammation of the pericardial space that results in an effusion that leads to hemodynamic compromise or required pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Cardiac tamponade/perforation	The development of a significant pericardial effusion during or within 30 days of undergoing the index AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromised (<80mmHg systolic bp), requires elective or urgent pericardiocentesis, or results in a 1cm or more pericardial effusion as documented by echocardiography.
Vascular access complications requiring intervention	Vascular access complication (e.g. groin hematoma, AV fistula, pseudoaneurysm) requiring intervention (e.g. surgical repair, blood transfusion).
Heart block	Impairment of AV conduction requiring permanent pacing intervention, if resulting from inappropriate ablation application.
Pulmonary vein (PV) stenosis	>70% diameter reduction of pulmonary vein from baseline CT/MRA scan.
Atrio-esophageal fistula	Connection between the atrium and the lumen of the esophagus as evidenced by documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium.

6.2 Secondary Safety Endpoints

1. The Primary Safety Endpoint assessed at 7 rather than 30 days
2. The proportion of subjects with a device- or procedure-related SAE
3. The proportion of subjects with stroke or TIA
4. The proportion of subjects requiring cardioversion
5. The proportion of subjects requiring an arrhythmia-related hospitalization

6.3 Primary Feasibility Endpoint

The proportion of subjects that achieve Acute Procedural Success (APS) defined as the percutaneous endocardial creation of a complete, electrically isolating set of lesions around the ostia of the pulmonary veins (PVI) using the FARAPULSE Endocardial Multi Ablation System during the Index Procedure, as clinically assessed by entrance and/or exit block performed ≥ 20 minutes after the last PVI lesion is made.

6.4 Secondary Feasibility Endpoints

1. The proportion of subjects who undergo the protocol-specified 75-Day Remapping Procedure and achieve Chronic Procedural Success (CPS) defined as persistent electrical isolation of all initially ablated pulmonary veins. Chronic Procedural Success will be subdivided by Index Procedure only CPS and Reablated CPS subjects.

2. The proportion of attempted subjects that achieve Acute CTI Success, defined as the creation of bi-directional electrical block across the CTI using the investigational devices.
3. Durability of the CTI and/or other extra-PV lesion set(s), when applicable. Durability is defined as unaltered integrity of each such lesion assessed at the Remapping Procedure.
4. The proportion of subjects that achieve Therapeutic Success, defined as freedom from:
   a. Post-Blanking Period through assessment: occurrence of AF, AFL or AT, or ablation for AF/AFL/AT using the study device
   b. At any time: ablation for AF/AFL/AT with a nonstudy device

   Therapeutic Success will be assessed from the end of the 90 Day Blanking Period through Months 6 and 12 and will be subdivided by on / off AFDs (Atrial Fibrillation Drugs) post-Blanking Period.

6.5 Additional Assessments

1. Proportion of subjects with early recurrence of atrial fibrillation (ERAF) by 90 days after the initial study ablation.
2. Time to Therapeutic Failure
3. Proportion of all ablated pulmonary veins that are isolated at the Index Procedure using the study device.
4. Proportion of all ablated pulmonary veins isolated using the study device during the Index Procedure that remain isolated at the 75-day Remapping Procedure.
5. The proportion of attempted subjects that achieve Chronic CTI Success, defined as persistent bi-directional electrical block across the CTI as assessed at the 75-day remapping procedure.
6. The proportion of attempted subjects that achieve Chronic Focal Success, defined as persistent electrical nonconductivity of extra-PV tissue targeted for ablation in the Index Procedure, excluding the CTI

6.6 Procedural Assessments

1) Assessments of duration for procedure components:
   a. Procedure time (initiation of venous access to venous access closure)
   b. Dwell time (sum of catheter entry-to-exit durations for each cardiac chamber)
   c. Total ablation time (first ablation to last ablation)
   d. Fluoroscopy time and dose (total duration and dose of exposure)
2) Characterization of lesion sets:
   a. PVI ablations
   b. Extra-PV ablations, excluding CTI ablations
   c. CTI ablations
   d. Anomalous PV ablations

7. Adverse Events, Device Effects, Malfunctions and Deficiencies

7.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
NOTE 4: This definition excludes medical conditions, findings or abnormalities present at the time of enrollment, which are defined as pre-existing conditions. Pre-existing conditions will not be included in the adverse event dataset. However, a worsening of a pre-existing condition during the study does constitute an adverse event.

7.2 Serious Adverse Events

A Serious Adverse Event (SAE) is an adverse event that led to:

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

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

7.3 Device Effects

7.3.1 Adverse Device Effects

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
NOTE 3: "Related to the uses of an investigational medical device" shall be defined for this protocol as a determination that the effects was probably or definitely related to an investigational device.

7.3.2 Serious Adverse Device Effects

A Serious Adverse Device Effect (SADE) is an adverse device effect (ADE) that has resulted in any of the consequences characteristic of a Serious Adverse Event. (SAE).

7.3.3 Unanticipated Serious Adverse Device Effects

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report as embodied in Section 4.1 of this CIP.

NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

NOTE 2: If an SAE is determined to be probably or definitely related to the device and has not been previously anticipated, the clinical finding would be classified as an unanticipated serious adverse device effect (USADE).

7.4 Device Deficiencies

A Device Deficiency is an inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

7.5 Use Errors

An Use Error is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

NOTE 1: Use error includes slips, lapses, and mistakes.

NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

7.6 Malfunctions

A Malfunction is a failure of an investigational medical device to perform in accordance with its design specifications and intended purpose when used in accordance with the instructions for use or the subject CIP.

7.7 Causality Relationship

The investigator will assess the causality of all adverse events in relation to the investigational device or any other study-related procedures according to five different levels of causality:

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;

- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably have explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

7.8 Reporting

AEs and SAEs:

All AEs, including all SAEs, will be monitored from the time of enrollment through discharge for this study. All AEs must be documented in the patient chart and recorded in the appropriate CRF. A description of the event, including the start date, resolution date, action taken and the outcome shall be provided along with the Investigator's assessment of the seriousness of the event and the relationship between the AE and the study devices and/or procedures.

All AEs should be followed until the event is resolved, judged to be chronically stable or 12 month study follow-up has been completed. The investigational site will provide relevant follow-up information to the Sponsor or designee upon request.

The investigator shall also report to the Sponsor or its designee any Device Deficiencies or Malfunctions that did not but might have led to a SAE if such an event were to recur.

The investigator shall notify the Sponsor and the designated CRO immediately and **not later than 24 hours** after the Investigator has become aware of a **SAE or Device Deficiency / Malfunction that might have led to a SAE.**

The Investigator shall report the SAE or Device Deficiency / Malfunction on the appropriate CRF

Should mail correspondence be necessary, documents can be sent to the following:

CRO: MedPass International SAS

Fax: +33 (0)1 40 53 81 11

Sponsor: FARAPULSE, Inc.

Email: clinical@farapulse.com

Contact: Mr. Christopher Schneider

Return of Subject Device:

In all cases, and whenever possible the device involved in the AE, SAE, Device Deficiency / Malfunction as described above is to be returned to the Sponsor or Sponsor's designee for analysis and investigation, as appropriate. The Study Coordinator shall contact the Sponsor for instructions on returning the device.

Device Deficiencies and Malfunctions:

All Device Deficiencies / Malfunctions that did not contribute and would not likely contribute to a SAE, shall be documented on the Device Deficiency / Malfunction CRF and submitted to the Sponsor **within 7 days** after the observed Device Deficiency / Malfunction. The Sponsor's Quality Assurance function shall ensure an assessment is completed for each reported Device Deficiency / Malfunction. Such information shall be provided in the final clinical report.

Depending on the local requirements or following agreement between both parties, the Sponsor, its designated representative (CRO) or the Principal Investigator will be responsible for performing safety reporting to the Ethics Committee according to the relevant local regulatory requirements.

The Sponsor or designated representative (CRO) will be responsible for reporting to the National Competent Authority according to national requirements in accordance with MEDDEV 2.7/3.

8. Monitoring

Clinical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the study in accordance with the Study Monitoring Plan.

The clinical monitors will evaluate compliance with the protocol, any specific recommendations made by the site's EC and the signed Investigator Agreement. Phone contacts and site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include a verification that the ICFwas properly obtained for all enrolled study participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the CRFs are in agreement with the source documentation and other records. The Investigator will make available to the clinical monitor for review all ICFs, all completed CRFs, source documentation and other relevant records for all enrolled subjects at the site.

If a deficiency is noted during an on-site monitoring visit or at any other time during the course of the study, the clinical monitor is required to discuss the situation with the Investigator and the Sponsor to ensure compliance.

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the study. The accuracy of all collected data will be verified for:

- Eligibility criteria
- Baseline characteristics
- Primary safety and feasibility endpoints
- Secondary endpoints
- Adverse events (including SAEs) and Device Deficiencies / Malfunction Reporting

Verification will utilize source documents including, but not limited to, medical records, office/ clinic notes, procedure reports, laboratory results, physician and nursing progress notes. Verification and quality of data, monitoring of clinical study progress and Investigator compliance with the approved protocol will be conducted by the Sponsor or its designated representative.

The Sponsor or its designated representative must be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. The monitor will review all source data and compare them to the data documented in the CRFs, in addition to performing a review of the Regulatory Site Binder, and assessing device accountability. The Investigator and / or institution will provide direct access to source data/ documents for study-related monitoring, audits, and regulatory review and inspection.

It is important that the Investigator and other relevant site personnel, including the research study coordinator, are available for consultation with the clinical monitors

during the monitoring visits and that sufficient time is devoted at the site for the monitoring process.

Additionally, telephone, email contact, and onsite visits will be conducted on a regular basis with the Investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the study.

If a deficiency is noted during the course of the study, the clinical monitor is required to discuss the situation with the site and the Sponsor (if required) to secure compliance. A Monitoring Site Visit Report will be issued to the Investigator and Sponsor.

9. Study Management

The Sponsor has overall responsibility for the conduct of the study according to Good Clinical Practice Guidelines (ICH E6 Consolidated Guidance to Good Clinical Practice) as well as any conditions imposed by local and national regulatory authorities.

For the subject investigation, the Sponsor will have direct responsibilities and will delegate other responsibilities to appropriate and qualified consultants, contractors and/ or CROs. Together, the Sponsor, consultants and CRO will ensure that the study is conducted according to the approved CIP, EC-approved ICF and all applicable governing regulations. All personnel to participate in the conduct of this clinical study will be qualified by education and/or experience to perform their tasks.

9.1 Key Contributors

9.1.1 Study Sponsor

FARAPULSE, Inc.
3715 Haven Ave. Suite 110
Menlo Park, CA 94025, USA
Phone: 617-686-7661
Email: kschneider@farapulse.com

9.1.2 CRO

MedPass International SAS
95b Boulevard Pereire
75017 Paris, France
Tel No: +33 1.42.12.83.30

9.1.3 Arrhythmia Core Lab

MDT – Medical Data Transfer, s.r.o.
Zabrdovicka 2, 615 00 Brno
Czech Republic
Contact: Veronika Bolkova
Tel: +420 725 069 195
iowa@mdtekg.cz

9.2 Ethical Considerations

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator shall avoid improper influence or inducement of the subject, monitor, other clinical investigator or other parties participating in or contributing to the clinical investigation.

9.2.1 Study Conduct

The study will be performed in accordance with the relevant parts of the Code of Federal Regulations, ICH Guidelines for Good Clinical Practices, the European Standard ISO 14155, the Declaration of Helsinki, and any regional and/or national regulations. The clinical investigation shall not begin until the required approval has been obtained from the National CA and the local EC. Any additional requirements imposed by the regulatory authority or EC shall be followed. These principles shall prevail over interests of science and society and shall be understood, observed and applied at every step in this clinical investigation.

9.2.2 Ethics Review

Before any subject can be enrolled in this study, the local or national EC and the CA must review and approve the CIP and the ICF to be used. A subject cannot be asked to sign the ICF until the study has been fully approved by the institution's EC and by the CA, if applicable. The Sponsor or their designated CRO will require a copy of any EC correspondence, as well as the final EC approval letter and the final EC-approved ICF, and approvals for the CIP and ICF revisions on amendments from the EC. The Sponsor or their designated CRO will keep all of the CA correspondence, as well as the CA approval letter.

9.2.3 Informed Consent

Subjects will not sign the ICF until the study has been fully approved by the institution's Ethics Committee and the Sponsor or their designated CRO has received and reviewed the specific EC-approved ICF. When the Investigator has determined the eligibility of a specific subject to enter the study, the ICF must be completed. The ICF must be read and understood by the subject, the subject's questions answered, and the form signed by the subject before any study-related procedures can be performed. All subjects are to receive copies of their signed ICF.

9.2.4 Coverage of Expenses

Study participants will be reimbursed for travel costs related to study hospital visits.

9.2.5 Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each subject participating in this study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor, CRO, Investigators and Site personnel will make every reasonable effort to protect the confidentiality of all subjects participating in the study.

9.3 Insurance

The Sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

9.4 Audits and Inspections

The Principal Investigator will also allow representatives of the governing EC, CA, U.S. Food and Drug Administration, and other applicable regulatory agencies to inspect all study records, CRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the CIP, completeness and exactness of the data being entered onto the CRFs and compliance with regulatory agency regulations.

The Principal Investigator will inform the Sponsor or the Sponsor's designee should they be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

9.5 Sponsor Responsibilities

Sponsor has the overall responsibility for the study and will:

- Select qualified Investigators, clinical investigators and study sites.
- Select qualified monitors.
- Provide the CIP and any subsequent amendments.
- Provide appropriate information and Investigational system training to the Investigator and study site staff.
- Ensure that all deviations from the CIP are reviewed with the appropriate Investigator(s) and reported on the CRFs and the final clinical report and that any necessary preventative or corrective action is taken.
- Ensure that all AEs and all ADEs are reported and reviewed with the Investigator(s), and where appropriate, that all SAEs and all SADEs are appropriately reported.
- Ensure that all Device Deficiencies / Malfunctions are reviewed by the Sponsor, and properly assessed and investigated, as appropriate.
- Promptly inform the Investigator and where applicable, any regulatory authorities, if the study is prematurely terminated or suspended and the reason for the termination or suspension.
- Ensure proper device usage, uniform data collection and protocol compliance.
- Provide site initiation training to include review of the FARAPULSE Endocardial Multi Ablation System Instructions for Use, the Clinical Investigation Plan, CRF instructions, CRFs, AE/SAE/Device Deficiency reporting and requirements for obtaining informed consent.
- Provide the FARAPULSE Endocardial Multi Ablation System to the participating study site, in quantities to support study activities.
- Coordinate ongoing communication with CROs, consultants and study site to resolve any problems concerning the protocol or data collection

- Every effort will be made to ensure compliance with the protocol.
- Retain ownership of all clinical data generated in this study and control the use of the data for purposes of regulatory submissions to CAs.
- Protect subject confidentiality.
- Provide Regulatory Site Binder to site.

9.6 Monitor Responsibilities

Clinical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the study.

Site Initiation Visit: Sponsor personnel and / or clinical monitors will conduct site initiation visits at the investigational site to ensure that the Principal Investigator and other investigational site personnel involved in the conduct of this investigation have received and understood the requirements and contents of this Clinical Investigation Plan, the Investigator's Brochure, the patient ICF, the CRFs, CRF Instructions, AE/SAE/Device Deficiency reporting requirements, and the Instructions for Use and the Institution and/ or Investigator Agreement.

Site Monitoring: The clinical monitors will conduct routine on-site monitoring visits and phone calls in accordance with a Study Monitoring Plan to evaluate compliance with the CIP, any specific recommendations made by the site's EC and the signed Institution and/or Investigator Agreement and to ensure that the CIP is being followed and that any protocol deviations are properly documented on the respective CRF. Clinical monitoring will include a verification that informed consent was properly obtained and documented for all enrolled study participants, a review of clinical records and CRFs for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents.

Clinical monitoring will include a review of all adverse events, SAEs and Device Deficiencies / Malfunctions to ensure that all information has been reported to the Sponsor, EC and regulatory authorities as required by the Clinical Investigational Plan and applicable standards and laws.

The clinical monitor will verify that the CRFs are complete and in agreement with the source documentation and other records. The clinical monitor will ensure that all CRFs have been signed and dated by the Investigator.

The Investigator will make available to the clinical monitor for review all ICFs, all CRFs, source documentation and other relevant records for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site for the monitoring process.

If a deficiency is noted during an on-site visit or at any other time during the course of the study, the clinical monitor is required to discuss the situation with the Investigator and the Sponsor, and to subsequently monitor the implementation of corrective actions that are required to address the situation.

All monitoring activities will be documented by the clinical monitor in a Monitoring Report and will include, at a minimum, the date, investigational site

visited, names of all personnel involved in the visit, a listing of all documents reviewed and a summary of all findings, facts, deviations, conclusions and recommended actions to be taken. Key findings will be reviewed with the clinical investigator.

Upon completion of the study, a study close out visit will be conducted to ensure that all data collection and study requirements are complete.

9.7 Investigator Responsibilities

At a minimum, the following documents will be provided by the investigational site to the Sponsor prior to study start (consent of the first subject):

- Signed Clinical Trial Agreements
- Signed Financial Disclosure Form
- Signed Clinical Investigation Plan Signature Page
- Investigator and Co-Investigator's current Curriculum Vitae
- Any other additional documents as required by the Sponsor

The Investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the CIP, governing regulations, data protection regulations, medical device laws, the Declaration of Helsinki and any other conditions imposed by the relevant regulatory authorities. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain original source documents from which study-related data are derived.

The Investigator(s) shall be responsible for the day to day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

The Investigator(s) shall:

- Have the qualified and trained resources to conduct the investigation properly.
- Obtain from the Sponsor the information which the Investigator(s) judges essential about the device and be familiar with this information.
- Be well acquainted with the CIP before signing the signature page.
- Support the monitor, auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the CRF where inconsistencies or missing values are identified.
- Discuss with the Sponsor management any question of modification of the CIP.
- Make sure that the CIP is followed by all responsible for the conduct of the study at his/ her institution. Any deviation shall be documented and reported to the study Sponsor and CRO.
- Make the necessary arrangements to ensure the proper conduct and completion of the investigation.
- Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject.

- Ensure that appropriate EC and CA approval is obtained prior to the start of the investigation.
- Inform Sponsor about adverse events and Device Deficiencies / Malfunctions in a timely manner; document on applicable CRFs.
- Endeavor to ensure an adequate recruitment of subjects.
- Ensure that the subject has adequate information and time to provide informed consent.
- Ensure that informed consent is obtained and documented on the EC-approved ICF.
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study.
- Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the CIP shall not require the prior approval of the Sponsor or the national and local regulatory authorities. Such deviations shall not be considered as a breach of agreement but shall be documented and reported to Sponsor.
- Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the investigation shall be made known to the Sponsor and, if pertinent to the safety or well-being of the subject, and the private clinician.
- Inform the subject and/ or the subject's physician about any premature termination or suspension of the investigation with a rationale for study termination.
- Have primary responsibility for the accuracy, legibility and security of all investigation data, documents and subject records both during and after the investigation.
- Sign each subject's CRF, as applicable.
- Be responsible for the supervision and assignment of duties at his/ her clinical center.
- Ensure that all investigational devices are kept in a secure location and that all Systems are accounted for on the Device Accountability Form (number of devices used, discarded and returned to Sponsor).
- Investigator shall assign responsibility of Regulatory Site Binder and its maintenance to the Research Study Coordinator.

9.8 Investigator Training

The participating investigator will be trained in the use of the FARAPULSE Endocardial Multi Ablation System prior to participating in the study. Device training will be conducted by the Sponsor or its representatives. All device training will be documented in a training log that will be maintained in the Regulatory Site Binder.

9.9 Site Training

To ensure accurate, complete and reliable data, the Sponsor or its representatives will provide instructional material to the site, as appropriate; instruct the

investigator and study personnel on the CIP, the completion of the CRFs including CRF Instructions, and study procedures; communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic monitoring visits to the site. During those visits, the Sponsor or its representatives will monitor the subject data recorded in the CRFs against the source documents at the site for all enrolled subjects.

9.10 Clinical Events and Data Monitoring Committee

The Sponsor has established an external group of expert physicians who are not investigators to serve as the Clinical Events and Data Monitoring Committee (CEDMC). This group will consist of a panel of 3 experienced, independent physicians who are not investigators and who will be supported by the Medical Monitor and Study Statistician. A combined CEDMC procedure is an appropriate structure for a 40 subject feasibility study.

The CEDMC will review and approve a Charter. The CEDMC will convene during the study to screen, classify and adjudicate all adverse events reported in the subject investigation as well as major study outcomes. The CEDMC will be provided with case summaries, relevant source documents and any other information required to evaluate and adjudicate the adverse events and study outcomes.

The CEDMC will also convene to review safety data and trends during the conduct of the study. This formal assessment will occur at a minimum after the enrollment of 20 and then 40 subjects. The CEDMC will recommend to the Sponsor whether a study pause or termination is required if it identifies a trend that indicates a danger to patient safety.

9.11 Data Management

Data management procedures will be included in the Study Management Plan.

CRFs will be made available to the participating site. Investigators are responsible for the accurate completion of patient CRFs during the study. The Investigator will ensure that complete, accurate and timely data on CRFs are completed, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. The Investigator is expected to maintain all source documents as required by the CIP, including laboratory results, supporting medical records, and signed ICFs. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed CRFs.

After CRF Monitoring has been complete and deficiencies / discrepancies resolved, CRFs will be provided to the Sponsor or CRO, and data from the study will be entered from the CRFs into a central database. CRF data will be reviewed to identify any inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the Investigator by the CRO.

9.12 Study Suspension or Early Termination

The study can be discontinued at any site at the discretion of the Investigator or study Sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events.
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary.
- Data demonstrates a benefit to subjects who undergo percutaneous ablation with the FARAPULSE Endocardial Multi Ablation System making treatment without the FARAPULSE Endocardial Multi Ablation System unethical.
- Insufficient recruitment of subjects.
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)
- Persistent non-compliance with the Clinical Investigation Plan.
- Persistent non-compliance with regulatory requirements.

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform the clinical investigator/ investigational center of the termination or suspension and the reason(s) for discontinuation / suspension. The national and local regulatory authorities shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor, CRO or by the clinical investigator/ investigation center. Further, if the study is discontinued or suspended prematurely, patients enrolled to that point will continue to be followed for safety through the 12-month timepoint.

9.13 Criteria for Suspending/ Terminating a Study Center

Sponsor reserves the right to stop the screening of subjects at the study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/ terminating the study center include, but are not limited to:

- Repeated failure to complete CRFs prior to scheduled monitoring visits;
- Failure to obtain written informed consent using the EC-approved ICF;
- Failure to report SAEs/ USADEs to Sponsor within 24 hours of knowledge;
- Loss of (or unaccounted for) investigational product inventory or repeated failure of device accountability.

9.14 Deviations from the Clinical Investigation Plan

The Investigator is not allowed to deviate from the approved CIP except in emergency circumstances.

The Investigator must notify the Sponsor and the CRO of any deviation from the CIP and document the reason for the deviation.

The Investigator shall notify the Sponsor and the reviewing EC of any deviation from the CIP, as per national requirements, to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five (5) working days after the emergency occurred.

10. Regulatory Considerations

10.1 Maintaining Records

The Sponsor and CRO will maintain copies of critical correspondence, regulatory approvals, Trial Master Files, clinical data, shipment of devices, adverse events, serious adverse events, serious adverse device effects and other records related to the clinical study.

Trial records will be maintained for a minimum of 3 years following the completion of research activities and closure of the study with Ethics Committees, whichever is longer.

10.2 Data Handling and Record Keeping

10.2.1 Source Documents

The Investigator must maintain detailed source documents on all subjects who are enrolled or who undergo screening in the study. Source documents include but are not limited to, subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests, hemodynamic studies).

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number.
- The Clinical Investigation Plan number and the name of the Sponsor.
- The date that Informed Consent was obtained and signed by the patient and Investigator.
- Evidence that the subject meets the study eligibility requirements (e.g., medical history, study procedures and/or evaluations).
- The dates of all study related subject visits.
- Evidence that required procedures and/or evaluations were completed.
- Use of any concurrent medications.
- Documentation of specific device used.
- Occurrence and status of any adverse events (AEs / SAEs)
- The date the subject exited the study and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation.

10.2.2 Data Collection

The Investigator must maintain detailed records on all subjects who sign the ICF and begin the pre-procedure evaluation. Data for enrolled subjects is transcribed onto CRFs provided by the Sponsor or designee. All data should be transcribed completely, promptly and legibly. Corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious). Original CRF pages will be collected by the Sponsor

or Sponsor's designee after they are reviewed by the study monitor. The investigator should maintain a copy of all completed CRFs from this study.

Study exit forms will be completed for all enrolled subjects, regardless if they did or did not complete the study (e.g., subject discontinuation, study termination). The Sponsor and investigational site will maintain all records pertaining to this study in accordance with local and national regulations. Prior to the destruction of study records the Investigator or his representative shall contact the Sponsor to ensure that they no longer need to be retained. In addition, Sponsor shall be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

10.3 Ethics Committee and Competent Authority Approval

Regulatory approvals must be obtained prior to enrollment of the first patient. The Sponsor is responsible for obtaining regulatory and local approvals for the study. The Sponsor or its designated representative will require a copy of any IC and CA correspondence, as well as the final approval letter from the EC and CA, where applicable.

An Investigator may not make CIP changes without prior approval by the Sponsor. All significant CIP changes that may affect the following must be submitted and approved by the EC and CA before initiating the change:

- Validity of the data or information resulting from the completion of the approved CIP
- Relationship of the likely subject risk to benefit relied upon to approve the CIP
- Scientific soundness of the CIP
- Rights, safety, or welfare of the human subjects involved in the investigation

The Sponsor will notify the investigational site of such changes to ensure the study continues to be conducted consistent with the approved CIP.

10.4 Procedure for Amending the CIP

The process of amending the CIP and/or related documents is the responsibility of the sponsor. The procedure for amending the CIP shall be as follows:

- The Sponsor, Investigator, or other relevant party (e.g. EC, CA, CEDMC) may recommend modification of the CIP.
- The Sponsor will then modify as necessary the CIP and any associated documents requiring amendment as a result of the modification(s).
- The Sponsor or designated CRO will then submit the revised CIP and any other affected documents to the EC and CA for approval, per regulation.
- Once all required approvals are obtained, the site will be trained to the latest approved version of the CIP and any other affected documents.

10.5 Device Accountability

The Investigator is responsible for maintaining a Device Accountability Log that will track device receipt, device usage for all subjects and device returns to Sponsor or designees. Information tracked will include date of device usage, subject ID, and lot number.

11. Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied to you that is indicated as confidential.

The data generated by this clinical study are the property of the Sponsor and should not be disclosed without the prior written permission of FARAPULSE, Inc. These data may be used by FARAPULSE, Inc. now and in the future for presentation or publication at FARAPULSE, Inc.'s discretion or for submission to governmental regulatory agencies. FARAPULSE, Inc. reserves the right of prior review of any publication or presentation of data from the subject investigation.

12. Bibliography

1 Page RL. Newly Diagnosed Atrial Fibrillation. *New England Journal of Medicine*, 351(23):2408–16, 2004.

2 Feinberg WM, Cornell ES, Nightingale SD, et al. Relationship between Prothrombin Activation Fragment F1.2 and International Normalized Ratio in Patients with Atrial Fibrillation. Stroke Prevention in Atrial Fibrillation

3 Fuster, V, Ryden, L, Asinger, R, et al. ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol*, 2001;38:1231-65.

4 Go AS, Hylek EM, and et al. Phillips KA. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (atria) study. *JAMA*, 285:2370–5, 2001.

5 Miyasaka Y., Barnes ME., et al. Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence. *Circulation.* 2006;114:119-125.

6 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983– 8.

7 Le Heuzey JY, Paziaud O, Piot O, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. *Am Heart J* 2004;147:121– 6.

8 Calkins, et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up. *Heart Rhythm* 2017; 14:e275-444.

9 Mont L, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). EurHeart J 2014;35(8):501–507

10 Al-Sakere B, Andre´ F, et al. Tumor Ablation with Irreversible Electroporation. *PLoS ONE* 2(11): e1135.

11 Neumcke, B., Walz, D., L~uger, P. 1970. Non linear effects in lipid bilayer membranes. III. The dissociation field effect. Biophys. J. 10:172

12 Benz R, Beckers F, Zimmermann U. Reversible electrical breakdown of lipid bilayer membranes: a charge-pulse relaxation study. J Membr Biol. 1979 Jul 16;48(2):181-204.

13 Chang, D. C. 1989a. Cell poration and cell fusion using an oscillating electric field. Biophys. J. 56:641-652.

14 D.C. Chang, T.S. Reese Changes in membrane structure induced by electroporation as revealed by rapid-freezing electron microscopy. Biophysical Journal, Volume 58, Issue 1, July 1990, Pages –12

15 Wendler JJ, Pech M, Blaschke S et al (2012) Angiography in the isolated perfused kidney: radiological evaluation of vascular protection in tissue ablation by nonthermal irreversible electroporation. Cardiovasc Intervent Radiol 35:383–390

16 Gehl J1, Skovsgaard T, Mir LM. Vascular reactions to in vivo electroporation: characterization and consequences for drug and gene delivery. Biochim Biophys Acta. 2002 Jan 15;1569(1-3):51-8.

17 Kingham TP, Karkar AM, D'Angelica MI et al (2012) Ablation of perivascular hepatic malignant tumors with irreversible electroporation. J Am Coll Surg 215:379–387

18 Olweny EO, Kapur P, Tan YK et al (2013) Irreversible electroporation: evaluation of nonthermal and thermal ablative capabilities in the porcine kidney. Urology 81:679–684

19 Maor E, Ivorra A, Leor J, Rubinsky B. Irreversible electroporation attenuates neointimal formation after angioplasty. IEEE Trans Biomed Eng. 2008 Sep;55(9):2268-74.

20 Thomson KR1, Cheung W, et al. Investigation of the safety of irreversible electroporation in humans. *J Vasc Interv Radiol.* 2011 May;22(5):611-21

21 Wittkampf FH1, van Driel VJ, et al. Feasibility of electroporation for the creation of pulmonary vein ostial lesions. *J Cardiovasc Electrophysiol.* 2011 Mar;22(3):302-9.

22 Van Driel VJ, Neven KG, Pulmonary vein stenosis after catheter ablation: electroporation versus radiofrequency. *Circ Arrhythm Electrophysiol*. 2014; 7(4):734-8.

23 Neven K, van Driel V, et al. Epicardial linear electroporation ablation and lesion size. *Heart Rhythm*. 2014; pii: S1547-5271(14)00459-7.