THE IMPACT STUDY: A SAFETY AND FEASIBILITY STUDY OF THE FARAPULSE CARDIAC ABLATION SYSTEM TO TREAT ATRIAL FIBRILLATION

ABBREVIATED TITLE: **"THE IMPACT STUDY"**

PROTOCOL NUMBER: CS0172-01, REVISION D

SPONSOR:
FARAPULSE, INC.
(FORMERLY IOWA APPROACH, INC.)
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1. Primary Study Contacts

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LEGAL REPRESENTATIVE	MedPass Limited Windsor House Bretforton, Evesham, Worcs. WR11 7JJ – United Kingdom

2. Executive Summary

SPONSOR NAME:	FARAPULSE, Inc.
TITLE OF TRIAL:	"The IMPACT Study: A Safety and Feasibility Study of the FARAPULSE Cardiac Ablation System to Treat Atrial Fibrillation" Abbreviated title "The IMPACT Study"
PROTOCOL NUMBER:	CS0172-01, REVISION D
OBJECTIVE:	The objective of the safety and feasibility trial is to demonstrate that the creation of electrically isolating lesions via pulsed electric field (PEF) ablation applied using the FARAPULSE Cardiac Ablation System during concomitant heart surgery is feasible and a safe treatment for paroxysmal atrial fibrillation (AF).
CLINICAL HYPOTHESIS:	Creation of electrically isolating lesions in cardiac tissue via ablation using the FARAPULSE Cardiac Ablation System during concomitant heart surgery is a feasible and safe treatment for paroxysmal AF.
NAME OF INVESTIGATIONAL DEVICE:	FARAPULSE Cardiac Ablation System • iowaPulse Cardiac Ablation Catheter System • iowaStar Generator System
DESIGN:	Prospective, single-arm, multi-center feasibility trial.
STUDY POPULATION	Subjects will be consented to undergo surgical PEF ablation using the FARAPULSE Cardiac Ablation System concomitant to heart surgery.
PLANNED ENROLLMENT:	Up to 25 subjects
CLINICAL SITES:	Up to 3 clinical sites in Europe

DURATION OF PARTICIPATION:	Subjects will be followed at 30 days, 3 months, 6 months and 12 months following the index surgical procedure with a blanking period for recurrent atrial fibrillation or atrial tachycardia of 3 months following the index surgical procedure. The enrollment period is estimated to take 6 months and subjects will be followed for up to 12 months for a total duration of approximately 18 months.
PRIMARY SAFETY ENDPOINT:	A composite safety endpoint consisting of the proportion of subjects that experience one or more of the following serious adverse events (SAEs) related to the investigational procedure and/or device within 30 days of the PEF ablation procedure or hospital discharge, whichever is later, except as noted below: • Cardiac death • Stroke and/or transient ischemic attack (TIA) • Myocardial infarction (MI) • Excessive bleeding • Atrio-esophageal fistula • Persistent post-surgical phrenic nerve paralysis at 12 months • Severe pulmonary vein stenosis (>70%)
SECONDARY SAFETY ENDPOINT:	The proportion of subjects reporting one or more SAEs for each follow-up interval. The intervals will include the period from: • the surgical procedure for the surgical ablation through the Day 30 follow-up visit; • the Day 30 follow-up visit through the Month 3 follow-up visit; • the Month 3 follow-up visit through the Month 6 follow-up visit; and • the Month 6 follow-up visit through the Month 12 follow-up visit.

PRIMARY FEASIBILITY ENDPOINT:	Proportion of subjects that achieve procedural success. Procedural success is defined as the creation of an electrically isolating "box" lesion encompassing the pulmonary veins and posterior left atrium using the study device. Specifically, the ability of the device to create a contiguous line of electrical block in the specified region of the left atrium.
SECONDARY FEASIBILITY ENDPOINTS:	The secondary feasibility endpoint(s) include: • Proportion of subjects that achieve long-term technical success. Long-term technical success is defined as electrical isolation of the pulmonary veins and posterior left atrium assessed at a follow-up electroanatomical remapping procedure performed 3-months post index procedure.
ADDITIONAL OBSERVATIONS:	Proportion of subjects that achieve therapeutic success. Therapeutic success is defined as freedom from AF, AFL (atrial flutter) and AT (atrial tachycardia, not including sinus tachycardia) following the blanking interval through Month 12.

INCLUSION CRITERIA

All subjects are required to meet all the following inclusion criteria to be considered eligible for participation in this trial:

1. Patients who are ≥ 18 and ≤ 70 years of age on the day of enrollment.
2. Diagnosis of paroxysmal atrial fibrillation.
3. Anteroposterior Left atrial diameter ≤ 5.5 cm as documented by transthoracic echocardiography (TTE) or computed tomography (CT) within 3 months prior to the procedure.
4. Subject has no contraindications to intraoperative transesophageal echocardiography;
5. Subject is scheduled to undergo elective on-pump cardiac surgical procedure(s) to be performed including open-heart surgery for one or more of the following:
   a. Mitral valve repair or replacement,
   b. Aortic valve repair or replacement
   c. Tricuspid valve repair or replacement, or
   d. Coronary artery bypass procedures
6. Left ventricular ejection fraction ≥40% as documented by TTE within 12 months prior to the procedure.
7. Received a standard cardiac work up and is an appropriate candidate for an investigational procedure as determined by trial investigators.
8. Subject is willing and capable of providing Informed Consent to undergo study procedures and participate in all examinations and follow-ups associated with this clinical trial.

EXCLUSION CRITERIA

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

1. Abnormal cardiac and/or epicardial anatomy (such as adhesion, anomalous coronaries, thickened epicardium, etc.) or pericardial reflections on TTE, MRI or CT.
2. Prior left-sided cardiac ablation.
3. Prior history of open chest surgery and/or any procedure where the pericardial space was entered or instrumented (pericardiocentesis, catheter mapping and /or ablation).
4. Patient has a prosthetic heart valve.
5. Patient has a left atrial appendage device

6. Prior history of pericarditis or pericarditis within 3 months based on the TTE examination.
7. Subject is a woman of child bearing age
8. Prior history of rheumatic fever.
9. Prior history of medical procedure involving instrumentation of the left atrium (previous ablation, Atrial septal defect) ASD closure, left atrial appendage occlusion)
10. History of severe chronic gastrointenstinal problems involving the esophagus, stomach and/or untreated acid reflux
11. History of abnormal bleeding and/or clotting disorder.
12. Active malignancy or history of treated cancer within 24 months of enrollment.
13. Clinically significant infection or sepsis.
14. History of stroke or TIA within prior 6 months
15. New York heart Association (NYHA) class IIIb or IV congestive heart failure and/or any heart failure hospitalization within 3 months prior to enrollment.
16. Body mass index > 35.
17. Estimate glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 or has ever received dialysis.
18. History of untreated and serious hypotension, bradycardia or chronotropic incompetence.
19. Any of the following within 3 months of enrollment:
    - Major surgery except for the index procedure
    - Myocardial infarction
    - Unstable angina
    - Percutaneous coronary intervention (e.g., CABG or PTCA)
    - Sudden cardiac death event
    - Left atrial thrombus that has not resolved as shown by TEE or CT
    - Implant of pacemaker, ICD or CRT.
20. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
21. History of pulmonary hypertension with Pulmonary systolic artery pressure >50 mm Hg, severe Chronic Obstructive Pulmonary Disease or restrictive lung disease.
22. Patients with any other significant uncontrolled or unstable medical condition (such as uncontrolled brady-arrhythmias, ventricular arrhythmias, hyperthyroidism or significant coagulation disorder).
23. Life expectancy less than one year.

24. Clinically significant psychological condition that in the physician's opinion would prohibit the subject's ability to meet the protocol requirements.
25. Enrolled in another cardiac clinical trial that would interfere with this trial.
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27. Clinically significant psychological condition that in the physician's opinion would prohibit the subject's ability to meet the protocol requirements.
28. Enrolled in another cardiac clinical trial that would interfere with this trial.

3. Introduction

3.1 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.[i,ii]. The incidence increases with advancing age, affecting 6% of the population over age 60 and 10% of the population over age 80[iii,iv]. Age-adjusted population trending projects 16 million people in the United States will have AF by 2050[v]. Atrial fibrillation remains a significant cause of morbidity and mortality in industrialized societies. The mortality rate for patients with atrial fibrillation is twice that of patients in whom normal sinus rhythm is maintained. The annual risk of AF related stroke is 5% per year and one of every six strokes diagnosed occurs in the presence of AF.[vi] 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). Last, AF remains an extremely costly public health burden, with annual per patient cost of care approaching €3000 (approximately U.S. $3200).[vii] Atrial fibrillation is characterized by abnormalities in electrical impulse formation or conduction within the heart; these abnormalities disrupt the heart's coordinated mechanical contraction and can result in reduced or insufficient cardiac output or other complications.[viii] Symptoms arising from this arrhythmia include palpitations, shortness of breath, fatigue, syncope, or intolerance to exertion.

According to the Heart Rhythm Society (HRS) 2012 Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, AF is clinically stratified by whether episodes are self-terminating (paroxysmal) or continuous (persistent or permanent AF).[ix] Paroxysmal AF (PAF) is defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days, or within 48 hours if terminated by pharmacologic or electrical cardioversion. Persistent AF is defined as continuous AF that is sustained beyond 7 days, or less than 7 days but terminated by pharmacologic or electrical cardioversion. Longstanding persistent AF is defined as continuous AF of greater than 12 months' duration. Permanent AF is defined as AF in a patient in whom a decision has been made not to restore or maintain sinus rhythm by any means.

Initial treatment of PAF is typically directed toward heart rate or rhythm control with drug therapy and direct current cardioversion (DCCV). As a reasonable alternative to restoring sinus rhythm via long-term pharmacologic therapy, catheter ablation is being performed with greater frequency. Three recent small randomized trials in patients with PAF demonstrated that catheter ablation was superior to antiarrhythmic therapy in the prevention of recurrent AF.[x,xi,xii] This was followed by the more recent Navistar ThermoCool® Catheter and EZ Steer ThermoCool® NAV Catheter PMA submission substantiating the findings in a larger series.[xiii]

Although it is still the consensus recommendation that catheter ablation should not be considered a first line therapy for atrial fibrillation[xiii], there is evidence that maintenance of sinus rhythm has important effects on mortality. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, in which 4,060 AF patients with high risk for stroke and death were randomized to either rhythm control or rate control by antiarrhythmic drugs, there were no significant differences in all-cause death between the two strategies.[xiv] However, a new on-treatment analysis of the AFFIRM study revealed that the presence of sinus rhythm was associated with a significant reduction in mortality, whereas the use of antiarrhythmic drugs increased mortality by 49%,[xv] suggesting that the beneficial effect of sinus rhythm restoration on survival might be offset by the adverse effects of antiarrhythmic drugs.

Ablation treatment paradigms have evolved over time, and current strategies emphasize isolation of the pulmonary veins (PVI) as the cornerstone of catheter ablation of AF. Energy sources for endocardial lesion creation have included radiofrequency, cryo (freezing), laser, ultrasound and microwave. New ablation techniques and devices continue to develop with the objective of improving safety and efficacy, while reducing procedure time (complexity). In elite single-center reports, the success rate for eliminating symptomatic AF (inclusive of both PAF and continuous AF subjects) varies from 55% - 77%, with many patients requiring multiple procedures.[xvi,xvii,xviii,xix] Retreatment rates as high as 40% have been reported.[xx]

Understanding the need for creating electrical isolation of the pulmonary veins, treatment paradigms have focused on creating circumferential lesions or wide circumferential lesion sets that block electrical continuity between the pulmonary veins and the left atrium. In a wide circumferential ablation (WACA) procedure, operators must form a contiguous line of electrical block around ipsilateral pulmonary veins using fluoroscopic guidance and electroanatomical mapping technologies. A limited assessment of lesion formation and position is determined by monitoring voltage reduction of the local electrogram at the target site. Electrical gaps in lesion sets occur frequently, leading to recurrent AF and/or creation of substrate susceptible to reentrant atrial tachycardias.[xxi] Ablation technologies that rely upon indirect assessment of lesion formation are challenged to deliver improved durability and therefore long-term efficacy of therapy.

3.2 Surgical Ablation:

The Maze Procedure involves open heart surgery on cardiopulmonary bypass. Areas of cardiac tissue are isolated, either by cut and sew methods or electrosurgically, creating a “maze” which prevents propagation of ectopic AF impulses[xxii, xxiii] notes: “While few patients are candidates for a stand-alone surgical procedure to cure AF using the maze or LA ablation techniques, these approaches can be an effective adjunct to coronary bypass or valve repair surgery to prevent recurrent postoperative AF.”

Reported failure rates for the maze procedure are as high as 30%. Jais 2002 summarized the conclusions from surgical treatments for AF.[xxiv]

- reduction of the atrial tissue mass available for fibrillation is effective in preventing maintenance of AF;
- the left atrium plays a dominant role in maintenance and initiation of AF;
- limited lesions placed around pulmonary veins can be as effective as complex ablation schema (maze)and safer.

However, Wisser 2007 reported results of a small non-randomized study comparing two groups of patients, all treated surgically for permanent AF at the same time as other major heart surgery. Group 1 (N=29) received a classic maze procedure: freedom from AF at 19 months follow up was 86%. Group 2 (N=43) received epicardial pulmonary vein isolation treatment, and freedom from AF at follow up was 59%. This difference was statistically significant.

3.3 Irreversible Electroporation (IRE):

Al-Sakere 2007[xxv] 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.[xxvi xxvii xxviii xxix] IRE ablation typically spares the extracellular matrix, which facilitates rapid wound healing.[xxx xxxi xxxii xxxiii xxxiv]

Thomson 2011[xxxv] reported a case-series study (N=38) assessing the safety of irreversible electroporation (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[xxxvi] (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[xxxvii] (N=6) confirmed this result out to 3-month follow up. Neven 2014[xxxviii] (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.

3.4 Complications of Catheter Based and Surgical Epicardial Ablation:

The risks and complications associated with thermal or non-thermal cardiac ablation depend on the complexity of the procedure. The most common complications due to cardiac ablations include bleeding, cardiac tamponade, stroke/TIA, pulmonary vein stenosis, phrenic nerve injury, thromboembolism, air embolism, post-procedural arrhythmias, and vascular complications. Further, recurrences of atrial fibrillation (AF) or atrial tachycardia after an initial AF catheter ablation procedure (20 – 40% of patients[xxxix]) are common.

Gelsomino 2014[xl] noted in a study of SAEs (Serious Adverse Event) rates for studies of convergent AF ablation (N=335) (Table 1). There were 3 early deaths (0.9%) and three conversions to sternotomy and cardiopulmonary bypass (0.9%). There were no late deaths or thromboembolic events. These SAE rates include both catheter ablation and epicardial ablation procedures in the reviewed studies. Expected adverse event rates from an isolated epicardial procedure are likely to be lower.

Table 1: Data from Gelsomino 2014 – Adverse Event Rates for Epicardial Ablation

Event	Frequency (%)
Bleeding	6 (1.8%)
Tamponade	4 (1.2%)
Pleural effusion	1 (0.3%)
Hemothorax	1 (0.3%)
Pneumothorax	1 (0.3%)
Pneumonia	1 (0.3%)

In conclusion, risks related to the FARAPULSE Cardiac Ablation System are expected to be no different from those of the products approved and available on the market for concomitant open-heart surgery, ablation procedures. FARAPULSE will be conducting bench and in-vivo testing to ensure safe use of the device during clinical investigation and ultimately compliance with Directive 93/42/EEC. FARAPULSE will also ensure, through its Risk Management System, that the residual and controllable risks have been minimized or eliminated.

4. Investigational Device

4.1 Name of Investigational Device

FARAPULSE Cardiac Ablation System.

4.2 Intended Use

The FARAPULSE Cardiac Ablation System is indicated for cardiac tissue ablation for the treatment of atrial fibrillation.

4.3 Classification

The FARAPULSE Cardiac Ablation System is comprised of the iowaPulse Cardiac Ablation Catheter System and the iowaStar Generator System.

The iowaPulse Cardiac Ablation Catheter System is classified as a Class III medical device. Per MEDDEV 2.4/1 Rev. 9 June 2010, Rule 6 applies to the ablation catheter, 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.

The iowaStar Generator System is classified as a Class IIb medical device. Per MEDDEV 2.4/1 Rev. 9 June 2010, 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.

4.4 System Components: FARAPULSE Cardiac Ablation System

The FARAPULSE Cardiac Ablation System used for this clinical investigation consists of the iowaPulse Cardiac Ablation Catheter System and iowaStar Generator System. Model numbers of the components used in this study are in Table 2: Components and Model Numbers of FARAPULSE Cardiac Ablation System.

Table 2: Components and Model Numbers of the FARAPULSE Cardiac Ablation System

Components & Sub Components	Model Number (REF#)
iowaPulse Cardiac Ablation Catheter System 1. Ablation Catheter 2. Cinch Tool	50T41
iowaStar Generator System 1. Pulsed Electric Field Generator (PEFG) 2. BNC Coaxial Cable	70T41

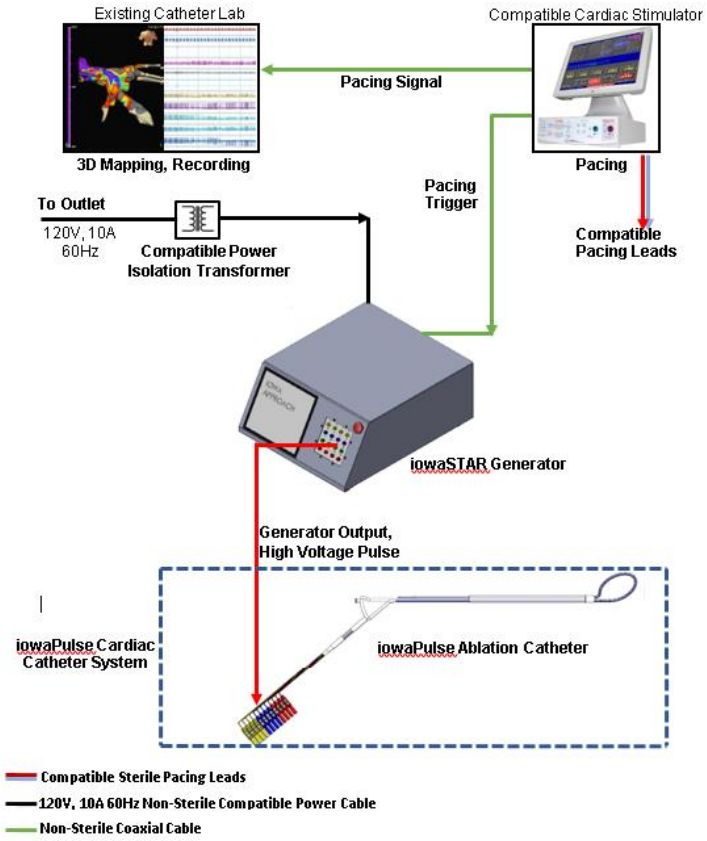


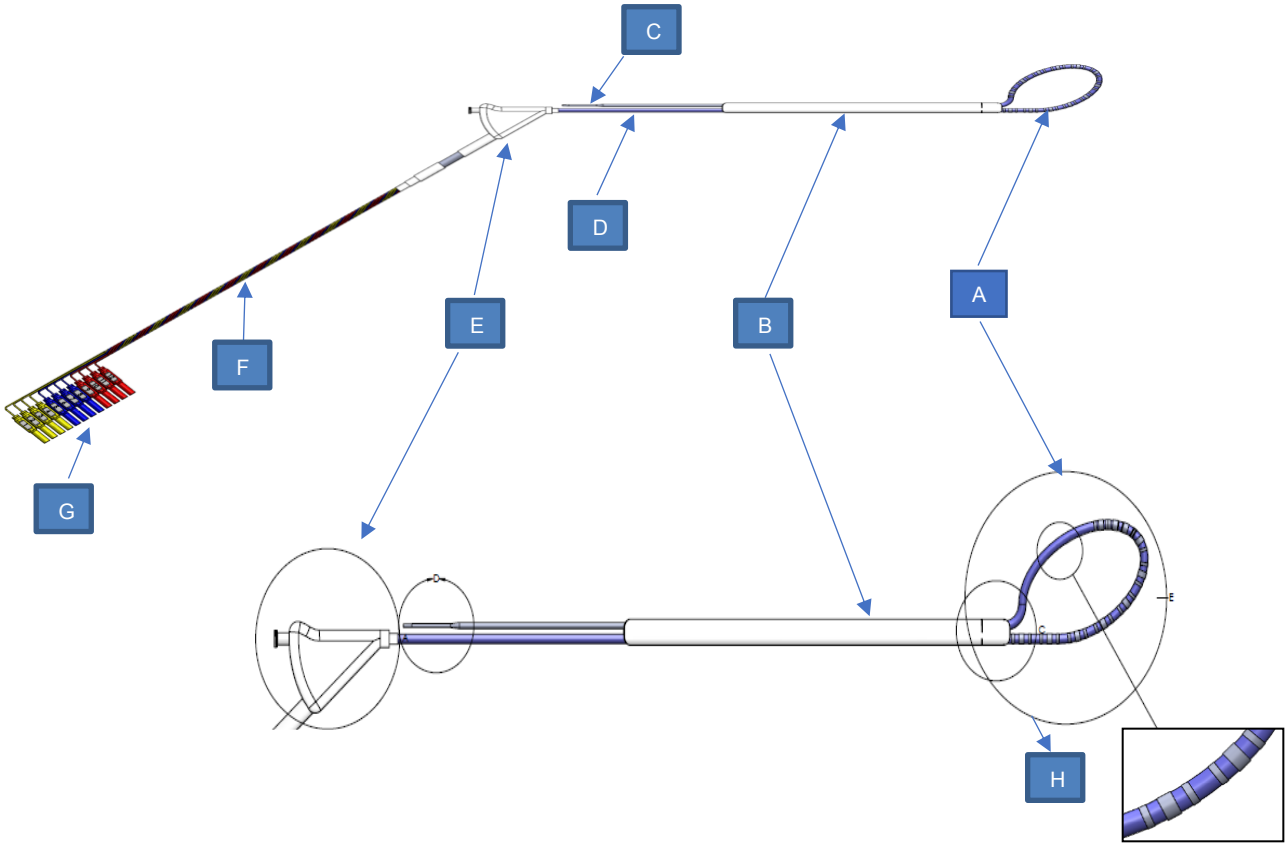
Figure 1: FARAPULSE Cardiac Ablation System and compatible device connections. The blue dotted box shows the sterile, single-use components of the system.

4.4.1 iowaPulse Ablation Catheter System

The iowaPulse Cardiac Ablation Catheter System consists of two (2) components: Ablation Catheter and Cinch Tool, which are used together. Both components are sterile and single use only (See Figure 2).

The Ablation Catheter is a multi-electrode catheter that connects electrically to the iowaStar Generator System. It has a total of 12 electrodes and each electrode of the ablation catheter consists of a triplet of electrode rings. The Catheter consists of a distal end, a midsection with electrodes and a proximal end feeding into the handle. The handle consists of a flush port and an extension cable with 12 color coded connectors. These (connectors 1 – 4 are yellow, connectors 5 – 8 are blue and connectors 9 – 12 are red) connect to the multi-channel iowaStar Generator System with the same color coding respectively. Pulsed Electric Field energy is delivered over a set of ablation catheter electrodes selected on a user interface.

The Cinch Tool comprises two parallel hollow tubes with an atraumatic distal tip.



A. Catheter Midsection (looped) – Ablation Catheter
B. Cinch Tool
C. Distal End – Ablation Catheter
D. Proximal End – Ablation Catheter
E. Handle with flush port
F. Extension Cable
G. 12 Connectors
H. Electrode Triplets

Figure 2: iowaPulse Cardiac Ablation Catheter System

4.4.2 iowaStar Generator System

The iowaStar Generator System is part of the FARAPULSE Cardiac Ablation System. It consists of two components – Pulsed Electric Field Generator (PEFG) and BNC Coaxial cable. The iowaStar Generator System is designed to deliver pulsed electric field energy to epicardial sites in the heart via the iowaPulse Cardiac Ablation Catheter System and other compatible devices (refer to IFU LBL0126 for the specific use and procedural steps of the iowaPulse Cardiac Ablation Catheter System and LBL0127 for other compatible devices). The iowaStar Generator System is indicated for use in conjunction with the iowaPulse Cardiac Ablation Catheter System.

The Pulsed Electric Field Generator is a 16-channel output unit that generates a pulsed voltage waveform that can be delivered over a set of user

selected ablation catheter electrodes. Determination of the active electrodes is defined by the physician at the time of treatment to optimize electrical contact with the treatment area. As an input, a compatible cardiac stimulator unit for cardiac pacing is applied to the surgical site via pacing leads and to the PEFG with a coaxial cable to synchronize the application of therapeutic energy to the actively paced heart. The PEFG interfaces with the physician to acknowledge proper synchronization. The BNC Coaxial Cable is one of the components, and it is used to connect the generator to a commercially available compatible cardiac stimulator/pacing device.

4.5 Device Accountability

The FARAPULSE Cardiac Ablation System will be housed 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 facility through use and/ or return or disposal.

The site will be responsible for keeping a Device Accountability Log provided by the Sponsor or its designated representative in which will be recorded, at a minimum, date of receipt, FARAPULSE Cardiac Ablation System identification number, expiration date, date of use, subject unique identity code and date of disposal of the device.

If there is a product malfunction or other need to return the system or system components to the Sponsor, the Sponsor should be contacted for safe product disposal and/ or return details.

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 in the Case Report Forms (CRFs) the lot numbers of the devices used during each case.

4.6 Return of Devices

All unused investigational devices will be returned to the study Sponsor upon completion of the clinical study. All used investigational devices will be returned to the study Sponsor for analysis. Any investigational device that fails to perform correctly will be equally returned to the study Sponsor for analysis. 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.

5. Trial Objectives

The objective of this feasibility and safety trial is to demonstrate that the creation of electrically isolating lesions generated by pulsed electric field

ablation using the FARAPULSE Cardiac Ablation System during concomitant heart surgery is feasible and a safe treatment for paroxysmal atrial fibrillation.

5.1 Study design

The IMPACT Study is a prospective, observational, multi-center, intention-to-treat study using the FARAPULSE Cardiac Ablation System in subjects with paroxysmal atrial fibrillation who consented to undergo surgical PEF ablation concomitant to heart surgery.

5.2 Selection and Withdrawal of Subjects

5.2.1 Inclusion Criteria

All subjects are required to meet all of the following inclusion criteria in order to be considered eligible for participation in this trial:

1. Patients who are ≥ 18 and ≤ 70 years of age on the day of enrollment.
2. Diagnosis of paroxysmal atrial fibrillation.
3. Anteroposterior Left atrial diameter ≤ 5.5 cm as documented by transthoracic echocardiography (TTE) or computed tomography (CT) within 3 months prior to the procedure.
4. Subject has no contraindications to intraoperative transesophageal echocardiography;
5. Subject is scheduled to undergo elective on-pump cardiac surgical procedure(s) to be performed including open-heart surgery for one or more of the following:
   - Mitral valve repair or replacement,
   - Aortic valve repair or replacement
   - Tricuspid valve repair or replacement, or
   - Coronary artery bypass procedures
6. Left ventricular ejection fraction ≥40% as documented by TTE within 12 months prior to the procedure.
7. Received a standard cardiac work up and is an appropriate candidate for an investigational procedure as determined by trial investigators.
8. Subject is willing and capable of providing Informed Consent to undergo study procedures and participate in all examinations and follow-ups associated with this clinical trial.

5.2.2 Exclusion Criteria

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

1. Abnormal cardiac and/or epicardial anatomy (such as adhesion, anomalous coronaries, thickened epicardium, etc.) or pericardial reflections on TTE, MRI or CT.
2. Prior left-sided cardiac ablation.
3. Prior history of open chest surgery and/or any procedure where the pericardial space was entered or instrumented (pericardiocentesis, catheter mapping and /or ablation).
4. Patient has a prosthetic heart valve.
5. Patient has a left atrial appendage device
6. Prior history of pericarditis or pericarditis within 3 months based on the TTE examination.
7. Subject is a woman of child bearing age
8. Prior history of rheumatic fever.
9. Prior history of medical procedure involving instrumentation of the left atrium (previous ablation, Atrial septal defect) ASD closure, left atrial appendage occlusion)
10. History of severe chronic gastrointenstinal problems involving the esophagus, stomach and/or untreated acid reflux
11. History of abnormal bleeding and/or clotting disorder.
12. Active malignancy or history of treated cancer within 24 months of enrollment.
13. Clinically significant infection or sepsis.
14. History of stroke or TIA within prior 6 months
15. New York heart Association (NYHA) class IIIb or IV congestive heart failure and/or any heart failure hospitalization within 3 months prior to enrollment.
16. Body mass index > 35.
17. Estimate glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 or has ever received dialysis.
18. History of untreated and serious hypotension, bradycardia or chronotropic incompetence.
19. Any of the following within 3 months of enrollment
    - Major surgery except for the index procedure
    - Myocardial infarction
    - Unstable angina
    - Percutaneous coronary intervention (e.g., CABG or PTCA)
    - Sudden cardiac death event
    - Left atrial thrombus that has not resolved as shown by TEE or CT
    - Implant of pacemaker, ICD or CRT.

20. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
21. History of pulmonary hypertension with Pulmonary systolic artery pressure >50 mm Hg, severe Chronic Obstructive Pulmonary Disease or restrictive lung disease.

22. Patients with any other significant uncontrolled or unstable medical condition (such as uncontrolled brady-arrhythmias, ventricular arrhythmias, hyperthyroidism or significant coagulation disorder).
23. Life expectancy less than one year.
24. Clinically significant psychological condition that in the physician's opinion would prohibit the subject's ability to meet the protocol requirements.
25. Enrolled in another cardiac clinical trial that would interfere with this trial.
26. Life expectancy less than one year.
27. Clinically significant psychological condition that in the physician's opinion would prohibit the subject's ability to meet the protocol requirements.
28. Enrolled in another cardiac clinical trial that would interfere with this trial.

5.3 Trial Design

5.3.1 Description of Trial Design

Prospective, single-arm, multi-center feasibility trial. Subjects will be consented to undergo surgical PEF ablation using the FARAPULSE Cardiac Ablation System concomitant to heart surgery. Subjects will be followed at 30 days, 3 months, 6 months and 12 months following the index surgical procedure with a blanking period for recurrent atrial fibrillation or atrial tachycardia of 3 months following the index surgical procedure.

5.4 Trial Endpoints

5.4.1 Primary Safety Endpoint

A composite safety endpoint consisting of the proportion of subjects that experience one or more of the following serious adverse events (SAEs) related to the investigational procedure and/or device within 30 days of the PEF ablation procedure or hospital discharge, whichever is later, except as noted below:

- Cardiac death
- Stroke and/or transient ischemic attack (TIA)
- Myocardial infarction (MI)
- Excessive bleeding
- Atrio-esophageal fistula
- Persistent post-surgical phrenic nerve paralysis at 12 months
- Severe pulmonary vein stenosis (>70%)

Table 3 summarized the primary safety endpoint definitions.

Table 3: Primary Safety Endpoint Definitions

Potential Serious Adverse Event	Definition
Cardiac Death	Excludes all non-cardiac deaths.
Stroke	A new focal neurological deficit of presumed vascular origin persisting more than 24 hours and with a neuro-imaging study that does not indicate a different etiology. All patients suspected of having a stroke will be evaluated by a neurologist and have appropriate imaging tests performed (CT or MRI) as determined by a neurologist. • The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours. • This stroke definition includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. • Stroke events in cases of blood disorders such as leukemia, and strokes secondary to trauma are excluded.
Transient Ischemic Attack (TIA)	A focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset. All patients suspected of having a TIA will be evaluated by a neurologist and have appropriate imaging tests performed (CT or MRI) as determined by a neurologist.
Myocardial Infarction* (MI)	The presence of any one of the following criteria: 1) detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB), which persist for more than one 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.
Excessive Bleeding*	Bleeding requiring re-operation or 2 units of PRBC transfusion within any 24 hours of the first 7 days following the index procedure.

Potential Serious Adverse Event	Definition
Atrioesophageal Fistula	An atrial esophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan are the most common methods of documentation of an atrial esophageal fistula.
Phrenic Nerve Paralysis*	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is defined as permanent if it persists for 12 months or longer following ablation.
Pulmonary Vein Stenosis*	A reduction of the diameter of a PV or first generation PV branch. PV stenosis can be categorized as mild <50%, moderate 50%-70%, and severe ≥70% based on the percentage reduction in the diameter of the PV or PV branch. A severe PV stenosis should be considered a major complication of AF ablation.

* 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design.

5.4.2 Secondary Safety Endpoint

The proportion of subjects reporting one or more SAEs for each follow-up interval. The intervals will include the period from:

- The surgical procedure for the surgical PEF ablation through the Day 30 follow-up visit;
- The Day 30 follow-up visit through the Month 3 follow-up visit;
- The Month 3 follow-up visit through the Month 6 follow-up visit; and
- The Month 6 follow-up visit through the Month 12 follow-up visit.

5.4.3 Primary Feasibility Endpoint

Proportion of subjects that achieve procedural success. Procedural success is defined as the creation of an electrically isolating “box” lesion encompassing the pulmonary veins and posterior left atrium using the study

device. Specifically, the ability of the device to create a contiguous line of electrical block in the specified region of the left atrium.

5.4.4 Secondary Feasibility Endpoints

The secondary feasibility endpoint(s) include:

- Proportion of subjects that achieve long-term technical success. Long-term technical success is defined as electrical isolation of the pulmonary veins and posterior left atrium assessed at a follow-up electroanatomical remapping procedure performed 3-months post index procedure.

5.4.5 Additional Observations

Proportion of subjects that achieve therapeutic success. Therapeutic success is defined as freedom from AF, AFL (atrial flutter) and AT (atrial tachycardia, not including sinus tachycardia) following the blanking interval through Month 12. Proportion of subjects that achieve therapeutic success. Therapeutic success is defined as freedom from AF, AFL (atrial flutter) and AT (atrial tachycardia, not including sinus tachycardia) following the blanking interval through Month 12. For subjects to be considered a therapeutic success, they will have to be free of a confirmed AF, AFL or AT episode lasting 30 seconds or more after completion of the blanking interval. If a qualifying episode of AF, AFL or AT is found during the 24-hour continuous ECG monitor at Months 6 or 12, during any scheduled or unscheduled 12-lead ECG, or during the use of an event monitor after the blanking interval, the subject will be considered a therapeutic failure. In addition, subjects will be considered a therapeutic failure if they have a repeat ablation procedure at any time through Month 12 or if they received DC cardioversion or Vaughan-Williams Class I or III antiarrhythmic drug therapy for the treatment or prevention of AF, AFL or AT after the end of the blanking interval through Month 12. However, subjects will not be considered therapeutic failures if they received DC cardioversion or Vaughan-Williams Class I or III antiarrhythmic drug therapy for treatment of non-AF arrhythmias during the blanking period. Finally, any subject death after the blanking interval and prior to the Month 12 visit will be adjudicated by the CEC. In the absence of evidence regarding the presence or recurrence of AF following the blanking period, these subjects will be considered lost to follow-up. If, on the other hand, there has been evidence of the presence or recurrence of AF following the blanking period, these subjects will be considered therapeutic failures.

5.5 Sample Size

Up to 25 subjects will be enrolled in this clinical trial.

5.6 Investigational Sites

The clinical trial will be conducted at up to 3 clinical sites in Europe.

5.7 Duration of Subject Participation

Subjects enrolled in the trial will participate for approximately 18 months. This includes the baseline evaluation, the procedure and follow-up evaluations at 1 month, 3 months, 6 months, 9 months and 12 months post-procedure.

5.8 Written Informed Consent

All subjects must provide written Informed Consent using the Ethics Committee approved Informed Consent Form before undergoing any study related procedures. Subjects cannot be asked to sign the Informed Consent document until the trial has been fully approved by the respective institution's EC and the Sponsor or their CRO representative has received and reviewed the specific EC-approved Informed Consent Form. Subjects who meet the general entry criteria will be asked to sign a Patient Informed Consent form 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. If the family of the subject is available, they should also be consulted. 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 consent form and discuss it with their family and physician. The subject shall be informed that his/ her participation in the clinical investigation is confidential. The Informed Consent Form must be read and understood by the subject and the subject's questions answered. The form must be signed and dated by both the subject and investigator conducting informed consent before the subject undergoes any study related procedures. All subjects are to receive copies of their signed and dated Informed Consent Form. A copy of the approved informed consent form along with a copy of each patient's signed consent form will be maintained by each Investigator in a designated clinical study administrative file. The subject and the investigator must sign the consent form prior to enrollment. 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 Patient Informed Consent form, 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 cardiac surgery 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.

5.9 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 informed consent.

Each subject will be assigned a unique study identification code to protect each subject's confidential health information. The unique study identity 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 each 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.

5.10 Withdrawal of Subjects

Subjects may voluntarily withdraw from the trial at any time for any reason. In addition, the investigator may withdraw the subject due to any of the following situations:

- adverse event (AE); or
- any other reason determined by the investigator to be in the best interest of the subject.

Subjects with an ongoing AE at the time of withdrawal should be followed on study until the clinical event has been resolved or is stable if at all possible.

5.11 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 trial.

5.12 Subject Confidentiality

All information concerning subjects or their participation in this trial will be considered confidential. Only authorized Sponsor and designated representative personnel and designated consultants and regulatory agencies will have access to these confidential files. Enrolled subjects will be assigned a unique, 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 case report forms. In addition, all patient identifiers except the unique anonymous identifier should be redacted from any x-ray and MRI images submitted from the participating site to the Sponsor or the Sponsor's designated reviewers for analysis.

5.13 Schedule of Events and Assessments

Subjects will complete the following visits and assessments as indicated below and in Table 4.

5.13.1 Baseline

The following baseline data will be collected:

- Medical history
- Medication history
- Pregnancy test (if applicable)
- 12-lead ECG
- Cardiac CT or MRI
- NYHA Classification
- TEE or other imaging modality for exclusion of left atrial thrombus

5.13.2 Procedure

For a detailed description of procedure workflow refer to LBL0026 and LBL0027. Procedural details will be captured in study CRF. The following procedural data will be collected:

- Medications administered
- Pre- and post-ablation electranatomical maps
- Anticoagulation monitoring (e.g. ACT)
- Adverse event(s)

5.13.3 Pre-Discharge

Prior to hospital discharge the following data will be collected:

- Use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications;
- Cardioversion(s) since surgery;
- For subjects on warfarin, assessment of INR therapeutic levels (maintain as clinically indicated);
- For subjects on dabigatran, perform a PTT and, if required, a thrombin time (Section 4.7.2.7 Anticoagulation Regimen);
- Cardiac rhythm as determined by a 12-lead ECG on day of hospital discharge;

- Heart failure status as assessed by NYHA classification on day of hospital discharge; and Adverse Events.

5.13.4 1 Month Follow-Up

Discharged subjects will return for an office visit 30 days (± 7 days) post-ablation treatment. Subjects that continue to be hospitalized 30 days post-ablation will have their 30-Day Follow-Up assessment performed at discharge. At a minimum, the following data will be collected at 30 Day Follow-Up visit:

- Use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications;
- Cardioversions since last visit;
- For subjects on anticoagulants, assessment of INR/PTT therapeutic levels (maintain as clinically indicated);
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit;
- Heart failure status as assessed by NYHA classification at the time of visit;
- Any hospital readmissions, including admission and discharge dates, since discharge from the original procedure; and

5.13.5 3 Month Follow-Up

Subjects will return for an office visit at the end of the blanking period (90 days ± 14 days post-ablation treatment). 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 treatment failures. Subjects are not permitted to undergo repeat ablation during the blanking period. If a repeat ablation procedure is performed during this time, the subjects will be considered a therapeutic treatment failure and exited from the study.

At a minimum, the following data will be collected at the end of the blanking period follow-up visit:

- Use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications;
- Cardioversions since last visit;
- Any additional ablation procedures performed;
- For subjects on anticoagulants, assessment of INR/PTT therapeutic levels (maintain as clinically indicated);
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit;

- Heart failure status as assessed by NYHA classification at the time of visit;
- Any hospital readmissions, including admission and discharge dates, since the previous visit; and
- Adverse events.
- If a subject is symptomatic for AF at the end of the blanking period, an event monitor will be provided to be used up to the 6-month follow-up visit to capture AF episodes.
- Patients will undergo an electroanatomical remapping procedure to assess electrical isolation of the posterior left atrium and pulmonary veins. Any electrical gaps may be closed at the investigator's discretion using a commercially approved ablation device. This will consist of placement of catheters in the left atrium via femoral access and transeptal puncture using conventional electrophysiology techniques.
- Patients will undergo a cardiac CT or MRI scan at 3 months to assess the patency of the pulmonary veins.

5.13.6 6 Month Follow-up

Subjects will return for an office visit 6 months (180 days ± 30 days) post-ablation treatment. At a minimum, the following data will be collected at 6 months:

- Use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications;
- Cardioversions since last visit;
- Any additional ablation procedures performed;
- For subjects on anticoagulants, assessment of INR/PTT therapeutic levels (maintain as clinically indicated);
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit;
- Heart failure status as assessed by NYHA classification at the time of visit;
- Cardiac rhythm as determined by a 24-hour continuous ECG monitor following the visit for subjects in NSR at the time of the visit;
- Any hospital readmissions, including admission and discharge dates, since the previous visit; and
- Adverse events.

5.13.6.1 Continuous ECG Monitor

- Each subject will be provided with a 24-hour continuous ECG monitor and will be instructed in its use.

- The monitoring service will be available to provide any necessary assistance with the use of the device and to reinforce the need to adhere to the protocol for the full 24 hours.

If a subject has symptomatic AF at the end of the 6-month follow-up visit, an event monitor will be provided to be used up to the 12-month follow-up visit to capture AF episodes.

5.13.7 12 Month Follow-Up

Subjects will return for an office visit 6 months (180 days ± 30 days) post-ablation treatment. At a minimum, the following data will be collected at 6 months:

- Use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications;
- Cardioversions since last visit;
- Any additional ablation procedures performed;
- For subjects on anticoagulants, assessment of INR/PTT therapeutic levels (maintain as clinically indicated);
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit;
- Heart failure status as assessed by NYHA classification at the time of visit;
- Cardiac rhythm as determined by a 24-hour continuous ECG monitor following the visit for subjects in NSR at the time of the visit;
- Any hospital readmissions, including admission and discharge dates, since the previous visit; and
- Adverse events.

5.13.7.1 Continuous ECG Monitor

- Each subject will be provided with a 24-hour continuous ECG monitor and will be instructed in its use.
- The monitoring service will be available to provide any necessary assistance with the use of the device and to reinforce the need to adhere to the protocol for the full 24 hours.
- If a subject has symptomatic AF at the end of the 6-month follow-up visit, an event monitor will be provided to be used up to the 12-month follow-up visit to capture AF episodes.

5.14 Unscheduled Visit

Any unscheduled follow-up visits that occur throughout the trial, 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:

- Use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications;
- Cardioversions since last visit;
- Any additional ablation procedures performed;
- For subjects on anticoagulants, assessment of INR/PTT therapeutic levels (maintain as clinically indicated);
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit;
- Heart failure status as assessed by NYHA classification at the time of visit;
- Any hospital readmissions, including admission and discharge dates, since the previous visit; and
- Adverse events.

5.15 Study Exit or Premature Withdrawal

Once the subject has completed the final follow-up visit they can be exited from the trial provided that they do not have any conditions that require continued follow-up.

Table 4: Summary of Trial Assessments

Assessment	Baseline	Procedure	30 Days Post-Procedure/ Discharge*	3 Month (End of Blanking Period)	6 Month	12 Month	Unscheduled
Visit Timeframe (days)			30±7	90±14	180±30	365±30	-
Medical History	X						
Medication History (current)	X						
Medications		X	X	X	X	X	X
Pregnancy test (for females of childbearing potential)	X			X			
12-lead ECG	X		X	X	X	X	X
24-Hour Continuous ECG Monitor (e.g., Holter)					X	X	
Cardiac CT or MRI	X			X			
3D Electroanatomical Mapping		X		X			
Event Monitor				X**	X**		
Record DC Cardioversions Since Last Visit			X	X	X	X	X
NYHA Classification	X		X	X	X	X	X
Fluoroscopic Examination of Diaphragm Motion						X**	
Objective Imaging Modality+	X[A+]						
Anticoagulation Monitoring		X**	X**	X**	X**	X**	X**
Adverse Events		X	X	X	X	X	X

* Whichever is later
** As needed
[A] Within 1 month
+ e.g., Transesophageal Echocardiogram (TEE), Transthoracic Echocardiogram (TTE), etc.

6. Risk Benefit Assessment

The Sponsor has conducted an analysis of the benefits and risks of the FARAPULSE Cardiac Ablation System and procedure. A detailed Risk Assessment has been completed, and the conclusion of this review is that this research study is justified because the overall potential benefit to the population outweighs its attendant risks.

6.1 Risks

The risk profile associated with the FARAPULSE Cardiac Ablation System and the ablation procedure is expected to be minimal and consistent with other similar devices currently in clinical use during concomitant heart surgery.

6.1.1 Potential Adverse Events

The following anticipated events have been identified as possible complications of cardiac surgery and atrial fibrillation ablation procedures and these and others may be associated with the FARAPULSE Cardiac Ablation System:

- Air embolism
- Anemia
- Arrhythmia, potentially requiring cardioversion
- Arteriovenous fistulae
- Arrhythmias, possibly requiring a pacemaker
- Drug allergic reaction or side effects (e.g., from contrast, steroids, analgesics, anesthetics, anticoagulants, sedatives, etc.)
- Back pain
- Bed sores
- Bleeding, hematoma, hemorrhage or aneurysm at vascular access sites
- Coronary artery or vein injury
- Cardiac tamponade
- Cardiac arrest or cardiac failure
- Catheter entrapment
- Cardiogenic shock
- Congestive Heart failure
- Coupling across/crossing of unintended structures
- Death
- Esophageal injury
- Hemorrhage
- Hemodynamic compromise
- Hemopericardium
- Hemoperitoneum
- Hemothorax
- Hypotension

- Increased defibrillation threshold
- Local infection, systemic infection, and/or sepsis
- Myocardial infarction / transient ischemia
- Nerve damage
- Organ failure
- Pain
- Perforation (e.g., of diaphragm, heart, liver, lung, and/or vessels).
- Pericardial irritation
- Pericardial effusion
- Pericarditis
- Peritonitis
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Pneumothorax
- 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 or open-heart surgery to remove retained catheter
- Thrombosis
- Thromboembolism
- Vessel damage, dissection, or occlusion.
- Phrenic nerve injury
- Conduction system injury resulting in sinus arrest or heart block, either transient or permanent

Concomitant medicinal and surgical treatments used during the procedure and follow-up phase of the clinical study include structural heart surgery for the index procedure, anticoagulation, and antiarrhythmic therapy. The FARAPULSE Cardiac Ablation System does not have any known interactions with these therapies.

6.2 Benefits

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

- The device system is used during concomitant heart surgery 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 tissue specific mechanism of ablation
- The device uses the standard open heart surgery technique.

- The device utilizes a standard irreversible electroporation generator to deliver energy in the form of ablation dose.

A fundamental difference between the FARAPULSE Cardiac Ablation System and other commercially released ablation systems used during concomitant heart surgery is that the pulsed electric field or irreversible electroporation energy is delivered through epicardial electrodes embedded in the catheter that surrounds the pulmonary veins.

As such, the potential risks are roughly equivalent to those associated with commercially released systems being used for cardiac ablation procedures during concomitant heart surgery. Currently, the complication rates for commercially available catheters are very 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 ultimately compliance with Directive 93/42/EEC. Some tests results are pending and will be released before this feasibility study.

The epicardial ablation capabilities of the system provide several potential benefits compared to commercially released systems, including reduced procedure time, reduced fluoroscopy time, faster healing, better safety and improved long-term clinical outcomes.

In-vivo research has demonstrated that the system performs as expected and supports the risk estimations used and verified effective risk mitigation. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels. The Sponsor has determined that the potential benefits of the system outweigh the potential risks and that the device is therefore safe for human use in the context of a clinical investigation.

There are no *guaranteed* benefits from participation in this study. It is also anticipated that once a physician learning curve is achieved, a reduced procedure and fluoroscopy time may be seen, since the energy delivery is done in 4 heart beats. Information gained from the conduct of this study may also be of benefit to other persons with the same medical condition.

7. Statistical Analysis and Endpoint Assessment

7.1 General Statistical Considerations

The primary objective of this study is to characterize the safety and feasibility of the FARAPULSE Cardiac Ablation System in subjects with paroxysmal atrial fibrillation undergoing cardiac surgery.

The study 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 design additional clinical studies.

All subjects will be followed on an intent-to-treat basis. The device performance will be assessed based on a per-protocol analysis of the primary safety and feasibility endpoints and secondary efficacy endpoints. An intent-to-treat analysis, along with other secondary analyses, will also be completed and reported.

Demographic, baseline clinical and disease characteristics, procedural results and primary, secondary and all additional endpoints will be summarized using descriptive statistics.

7.2 Sample Size Justification

The IMPACT Study is a first-in-man trial and as such a relatively small number of patients, up to 25, will be studied at up to three sites. The safety and feasibility of the device will be analyzed before embarking on larger fully powered clinical studies to analyze safety and efficacy of the FARAPULSE Cardiac Ablation System.

7.3 Demographic, Safety, Feasibility and Efficacy Data

Demographic and baseline clinical and disease characteristics will be summarized in tables. For continuous variables, the summary will include number, mean, and standard deviation and 95% confidence intervals. Summaries for categorical variables will include the number and percent of subjects in each category.

7.4 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.

7.5 Data Pooling

Data will be pooled from all trial sites. The basis for pooling is the clinical basis described in Meinert[xli] based on three critical features: all sites used the same protocol, the Sponsor monitored the sites to assure protocol compliance, and the sites all used the same data gathering mechanism (CRFs and data entry methods).

7.6 Assessment of Feasibility

7.6.1 Primary Feasibility Endpoint

Proportion of subjects that achieve procedural success. Procedural success is defined as the creation of an electrically isolating “box” lesion encompassing the pulmonary veins and posterior left atrium using the study device. Specifically, the ability of the device to create a contiguous line of electrical block in the specified region of the left atrium.

7.6.2 Secondary Feasibility Endpoint

The secondary feasibility endpoint(s) include:

- Proportion of subjects that achieve long-term technical success. Long-term technical success is defined as electrical isolation of the pulmonary veins and posterior left atrium assessed at a follow-up electroanatomical remapping procedure performed 3-months post index procedure.

7.7 Assessment of Safety

7.7.1 Primary Safety Endpoint

A composite safety endpoint consisting of the proportion of subjects that experience one or more of the following serious adverse events (SAEs) related to the investigational procedure and/or device within 30 days of the PEF ablation procedure or hospital discharge, whichever is later, except as noted below:

- Cardiac death
- Stroke and/or transient ischemic attack (TIA)
- Myocardial infarction (MI)
- Excessive bleeding or
- Atrioesophageal fistula
- Persistent post-surgical phrenic nerve paralysis at 12 months
- Severe pulmonary vein stenosis

All adverse events (AEs) will be adjudicated for seriousness as well as device and procedure relatedness.

7.7.2 Secondary Safety Endpoint

The proportion of subjects reporting one or more SAEs for each follow-up interval. The intervals will include the period from:

- the surgical procedure for the surgical PEF ablation through the Day 30 follow-up visit;
- the Day 30 follow-up visit through the Month 3 follow-up visit;
- the Month 3 follow-up visit through the Month 6 follow-up visit; and
- the Month 6 follow-up visit through the Month 12 follow-up visit.

7.8 Final Clinical Report

A final clinical report will be prepared at the conclusion of the trial. Copies of the final report will be provided to each investigator and to the respective IRBs/ECs.

8. Adverse Events and Serious Adverse Events

8.1 General

Adverse Event (AE):

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.

Serious Adverse Event (SAE):

- led to death,
- led to 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,
    - led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: 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.

Adverse Device Effect (ADE):

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

Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

Unanticipated Serious Adverse Device Effect (USADE):

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.

NOTE: 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.

Device Deficiency:

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.

Use error:

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.

Malfunction:

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

Causality relationship:

The investigator will assess the causality of all adverse events in relation to the research, i.e., the relationship between the AE / SAE and the investigational device or any other study-related procedures.

Each SAE will be classified 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.

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 adverse device effect (UADE). An UADE is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.”

8.2 Adverse Event Reporting

All AEs, including all SAEs, will be monitored from the time of enrollment through discharge for this trial. All AEs must be recorded in the patient chart and Case Report Form (CRF). A description of the event, including the start date, resolution date, action taken and the outcome should be provided along with the Investigator’s assessment of the relationship between the AE and the trial device.

All AEs should be followed until the event is resolved or judged to be chronically stable. The investigational site will provide relevant follow-up information to the Sponsor upon request.

The investigator should report to the Sponsor or its designee the following events, whether expected or not, in the corresponding sheet of the CRF, with the exception of AEs / SAEs detected before the patients has signed the patient consent form.

- AE

- SAE
- Device Deficiencies that did not but might have led to a SAE if:
  - Suitable action has not been taken or
  - Intervention had not been made or
  - If circumstances had been less fortunate
  - New findings/updated in relation to already reported events.

If an AE / SAE is present at the beginning of study prior to the subject providing signed consent to participate in the study, only its worsening should be reported.

The investigator shall notify the sponsor and the CRO immediately and not later than 24 hours after the investigator has become aware of a SAE or device deficiency that might have led to a SAE via the Adverse Event Form of the CRF.

This reporting should be done by faxing completed CRF pages to the CRO:

CRO: MedPass International SAS
Fax: +33 (0)1 40 53 81 11

Sponsor: FARAPULSE, Inc.
Fax: +1 650 489 1153
Email: kschneider@farapulse.com
Contact: Mr. Christopher Schneider

In the case of a SADE, when possible, the device involved in the failure or malfunction is to be returned to the Sponsor for analysis.

8.3 Reporting to Ethics committee / Competent Authority

Depending on the local requirements or following agreement between both parties, the sponsor, its designated representative 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 will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/3.

9. Monitoring

9.1 Trial Monitoring

Clinical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial. The clinical monitors will evaluate compliance with the protocol, any specific recommendations made by the site's Ethics Committee (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 Informed Consent Form was properly obtained for all enrolled trial 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 Case Report Forms (CRFs) are in agreement with the source documentation and other records. The investigator will make available to the clinical monitor for review all Informed Consent documents, all completed 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 trial, 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 trial. The accuracy of all collected data will be verified for:

- Eligibility criteria
- Baseline characteristics
- Primary safety and feasibility endpoints
- Adverse events
- Secondary endpoints

with 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 case report forms, in addition to performing a review of the Regulatory Binde, and conducting device accountability. The Investigator and/ or institution will provide direct access to

source data/ documents for trial-related monitoring, audits, and regulatory review and inspection.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the 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 trial.

If a deficiency is noted during the course of the trial the clinical monitor is required to discuss the situation with the site and the Sponsor (if required) to secure compliance.

10. 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 this study, Sponsor will have direct responsibilities and will delegate other responsibilities to appropriate and qualified consultants, contractors and/ or Contract Research Organizations (CROs). Together, the Sponsor, consultants and CROs will ensure that the study is conducted according to the Clinical Investigational Plan and all applicable and governing regulations. All personnel to participate in the conduct of this clinical trial will be qualified by education and/ or experience to perform their tasks.

10.1 Key Contributors

10.1.1 Study Sponsor

FARAPULSE, Inc.

3715 Haven Ave. Suite 110

Menlo Park, CA 94025, USA

Phone: 650-422-3633

Email: kschneider@farapulse.comCRO

MedPass International SAS

95b Boulevard Pereire

75017 Paris, France

Tel No: +33 1.42.12.83.30

10.1.2 Clinical Sites

A complete listing of all clinical sites will be maintained by the Sponsor and will be available upon request.

10.2 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(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

10.2.1 Trial Conduct

The trial 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 relevant national regulatory authority and the local Ethical Committee. 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.

10.2.2 Ethics Review

Before any subject can be enrolled in this trial, the IRB or EC for the specific institution must review and approve the protocol and the Informed Consent Form to be used. A subject cannot be asked to sign the Informed Consent Form until the trial has been fully approved by the institution's Ethics Committee. The Sponsor or their designated CRO (MedPass International) will require a copy of any Ethics Committee correspondence, as well as the final Ethics Committee approval letter and the final Ethics Committee approved Informed Consent Form and approvals for protocol and ICF revisions on amendments from each Ethics Committee.

10.2.3 Informed Consent

Subjects cannot be asked to sign the Informed Consent document until the trial has been fully approved by the respective institution's Ethics Committee and the Sponsor or their CRO representative has received and reviewed the specific Ethics Committee-approved Informed Consent Form. When the investigator has determined the eligibility of a specific subject to enter the trial, the Informed Consent Form must be completed. The consent form 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 Informed Consent Form.

10.2.4 Coverage of Expenses

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

10.2.5 Confidentiality

Confidentiality of subjects will be maintained throughout the trial. A unique identification code will be assigned to each subject participating in this trial. 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 and their CRO representative will make every reasonable effort to protect the confidentiality of all subjects participating in the trial.

10.3 Insurance

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

10.4 Audits and Inspections

The principal investigator will also allow representatives of the governing EC, Competent Authority (CA), the U.S. Food and Drug Administration (FDA), 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 trial. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being entered onto the CRFs and compliance with FDA or other 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.

10.5 Protocol Modifications

Any modification to the protocol, which may have an impact on the conduct of the study, or may affect patient safety, including changes of the study objectives, study design, patient population, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such amendments will be agreed upon by the Sponsor, the investigator and the appropriate regulatory bodies prior to implementation. A justification statement shall be included with each amended section of the amended document. The version number and date of amendments will be documented.

Administrative changes to the protocol are those that are thought to be minor corrections and/or clarifications, which have no impact on the way the study is conducted. These administrative changes will be agreed upon by the Sponsor and the investigator. The appropriate regulatory bodies will be notified in writing of administrative changes as required by local regulations.

In situations requiring a deviation from the protocol, the investigator or other physician in attendance will contact the Sponsor, if possible before implementing any deviation to the protocol, and the Sponsor may issue a

prospective protocol waiver. The CRF and source documentation must describe any deviation from the protocol.

10.6 Sponsor Responsibilities

Sponsor has the overall responsibility of the study and will:

- Select qualified Principal Investigators, clinical investigators and study sites
- Select qualified monitors
- Provide the Investigational Plan and any subsequent amendments
- Provide appropriate information and System training to Investigators and study site staff
- Ensure that all deviations from the Investigational Plan are reviewed with the appropriate Investigator(s) and reported in the CRF and the final report and that any necessary preventative or corrective action is taken
- Ensure that all adverse events and all adverse device effects (ADEs) are reported and reviewed with the Investigator(s), and where appropriate, that all serious adverse events (SAEs) and all serious adverse device effects (SADEs) are appropriately reported
- During the course of the investigation, inform in writing all Investigators about adverse events and adverse device effects that have been reported to Sponsor (this information shall be sent to each Investigator based on perceived risk)
- Promptly inform the Investigators 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 protocol initiation training to include review of the FARAPULSE Cardiac Ablation System instructions for use, the Investigational Plan, CRF completion guidelines, and guidelines for obtaining informed consent
- Provide the FARAPULSE Cardiac Ablation System to participating study sites, in quantities to support study activities
- Coordinate ongoing communication with CRO(s), consultants and study sites 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.

10.7 Monitor Responsibilities

The Sponsor has contracted MedPass International as the Clinical Monitor to support the Sponsor in implementing and monitoring the clinical investigation until its termination. Clinical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial.

Clinical monitors will conduct site initiation visits at each 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 investigational protocol, the Investigator's Brochure, the patient informed consent form, the CRFs, the Instructions for Use and the institution and/ or investigator agreement.

Clinical monitors will ensure that the site facilities are adequate for the conduct of this investigation and that resources, laboratories, equipment and personnel remain adequate throughout the investigation.

The clinical monitors will conduct routine on-site monitoring visits and phone calls to evaluate compliance with the protocol, any specific recommendations made by the site's Ethics Committee (EC) and the signed Institution and/or Investigator Agreement and to ensure that the protocol is being followed and that any protocol deviations are properly documented on respective form. Clinical monitoring will include a verification that Informed Consent Form was properly obtained for all enrolled trial participants, a review of clinical records 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 and device malfunctions to ensure that all information has been reported to the sponsor, EC and regulatory authorities as required by this investigational plan and applicable standards and laws.

The clinical monitor will verify that the Case Report Forms (CRFs) are complete and in agreement with the source documentation and other records. The clinical monitor will ensure that all CRFs have been electronically signed and dated by the investigator.

The investigator will make available to the clinical monitor for review all Informed Consent documents, all completed 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 trial, 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 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.

10.8 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 Investigational Plan Signature Page
- Relevant regulatory approvals
- 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 study protocol, governing regulations, data protection regulations, the 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 resources to conduct the investigation properly
- Ensure that conducting the investigation will not give rise to a conflict of interest
- 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 Clinical Investigation Protocol (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
- 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 regulatory approval is obtained prior to the start of the investigation
- Provide regulatory approvals to the Sponsor
- Inform Sponsor about adverse events in a timely manner
- Endeavor to ensure an adequate recruitment of subjects
- Ensure that the subject has adequate information to give informed consent
- Ensure that informed consent is obtained and documented
- 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 (number of devices used, discarded and returned to Sponsor).

10.9 Investigator Training

All participating investigators will be trained in the use of the FARAPULSE Cardiac Ablation System prior to participating in the trial. 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 site regulatory binder.

10.10 Site Training

To ensure accurate, complete and reliable data, the Sponsor or its representatives will provide instructional material to the sites, as appropriate; instruct the investigators and study personnel on the protocol, the completion of the CRFs, and trial 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.

10.11 Clinical Events Committee

A Clinical Events Committee (CEC) will convene during the study to classify and adjudicate all procedure-related and serious adverse events reported in this clinical study. The CEC will consist of physicians who have no formal involvement or conflict of interest with the subjects, the investigators, the designated CRO, and will be appointed by the Sponsor. The CEC will be provided with case summaries and relevant source documents in order to adjudicate the adverse events.

10.12 Data Management

Standardized CRFs will be provided to all participating sites. Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered from the CRFs into a central database. Incoming data will be frequently reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the investigator by the CRO. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent Forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed CRFs.

10.13 Study Suspension or Early Termination

The study can be discontinued 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 cardiac surgery with the FARAPULSE Cardiac Ablation System making treatment without the FARAPULSE Cardiac 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 protocol
- Persistent non-compliance with regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s)/ investigational center(s) of the termination or suspension and the reason(s) for this. 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 or by the clinical investigator/ investigation center(s).

In the event that the clinical study is terminated prematurely or suspended for any reason, the principal investigator will inform the study subjects, will assure appropriate therapy and follow-up for the subject, and, where required by applicable policies, will inform the regulatory authorities.

10.14 Criteria for Suspending/ Terminating a Study Center

Sponsor reserves the right to stop the screening of subjects at a 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 a study center include, but are not limited to:

- Repeated failure to complete case report forms prior to scheduled monitoring visits;
- Failure to obtain written Informed Consent;
- Failure to report SAEs/ UADEs to Sponsor within 24 hours of knowledge;
- Loss of (or unaccounted for) investigational product inventory.

10.15 Final Report

A Final Report will be prepared even if the study is prematurely terminated. The Final Report will be submitted to each participating Investigator, and regulatory agencies, as required.

10.16 Deviations from the Investigational Plan

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol. Except under defined circumstances, the investigator is not allowed to deviate from the clinical investigation plan.

Investigators shall be required to obtain prior approval from FARAPULSE before knowingly deviating from the protocol, except where necessary to protect the rights, life or physical well-being or safety 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. Except in such an emergency, prior approval by the Sponsor is required for changes in or deviations from a plan and, if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval of the Ethics Committee and regulatory authorities (e.g., FDA in the U.S.) is also required. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported through the appropriate CRF.

Deviations must be reported to FARAPULSE regardless of whether medically justifiable, pre-approved by FARAPULSE or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to FARAPULSE. Investigators will also adhere to procedures for reporting study deviations to their EC and CA, where required, in accordance with their specific reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

11. Regulatory considerations

11.1 Maintaining Records

The Sponsor will maintain copies of critical correspondence, clinical data, shipment of devices, serious adverse device effects and other records related to the clinical trial.

11.2 Data Handling and Record Keeping

11.2.1 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 subject medical records, hospital charts, clinic charts, investigator subject trial 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 trial and the subject number
- The trial protocol number and the name of the Sponsor
- The date that Informed Consent was obtained
- Evidence that the subject meet the trial eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all trial 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)
- The date the subject exited the trial and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation.

11.2.2 Data Collection

The investigator must maintain detailed records on all subjects who sign the Informed Consent Form and begin the pre-procedure evaluation. Data for enrolled subjects will be transcribed on to CRFs provided by the Sponsor. 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 trial.

Trial exit forms will be completed for all enrolled subjects, regardless if they did or did not complete the trial (e.g., subject discontinuation, trial termination). The Sponsor and clinical sites 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 should contact the Sponsor to ensure that they no longer need to be retained. In addition, Sponsor should 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.

11.3 Ethics Committee (EC) and Competent Authority (CA) Approval

Regulatory approvals must be obtained prior to enrolment 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 Ethics Committee and Competent Authority correspondence, as well as the final approval letter from the Ethics Committee and Competent Authority, where applicable.

An Investigator may not make protocol changes without prior approval by Sponsor. All significant protocol changes that may affect the following must be submitted and approved by the Ethics Committee and Competent Authority before initiating the change:

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

The Sponsor may make certain administrative changes to the protocol without prior approval of the relevant Ethics Committee and Competent Authority. The Sponsor will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites.

11.4 Device Accountability

The investigator will be responsible for maintaining a device accountability log that will track device usage for all subjects. Information tracked will include date of device usage, subject ID, lot number and the occurrence of any device malfunctions or failures.

12. Publication Policy

The existence of this clinical trial is confidential, and it should not be discussed with persons outside of the trial. Additionally, the information in this document and regarding this trial 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 trial 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 trial 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 this trial.

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