CONVERGE

CONVERGENCE OF EPICARDIAL AND ENDOCARDIAL RF ABLATION FOR THE TREATMENT OF SYMPTOMATIC PERSISTENT AF

PROTOCOL NO.: **VAL-1200(E)**

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SPONSOR SIGNATURES

Protocol Name:	**CONVERGE Pivotal Study**
Protocol Number:	**VAL-1200 (E)**
Protocol Title:	**Convergence Of Epicardial And Endocardial RF Ablation For The Treatment Of Symptomatic Persistent AF**
Investigations(Device:	**EPi-Sense®--AF Guided Coagulation System with VisiTrax®**

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October 02, 2017 **CONFIDENTIAL**

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1.0 INVESTIGATIONAL PLAN SUMMARY

1.1 Study Purpose

The purpose of this randomized pivotal study is to evaluate the safety and efficacy of the EPi-Sense®-AF Guided Coagulation System with VisiTrax® to treat symptomatic persistent Atrial Fibrillation (AF) patients who are refractory or intolerant to at least one Class I and/or III AAD. For the purposes of this study:

Refractory to Class I and/or III AAD will be defined as drug used that did not result in the absence of AF or atrial flutter (AFL);

Intolerant to Class I and/or III AAD will be defined as drug that patient was unable to tolerate and/or the side effects listed in the manufacturer's instructions for use were observed in the patient during the AAD drug therapy.

Persistent AF will be defined according to the Heart Rhythm Society (HRS) "HRS 2012 Expert Consensus Statement on Catheter and Surgical Ablation of AF".

- Persistent AF is defined as continuous AF that is sustained beyond 7 days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
  Persistent AF to be documented by:
  - Physician notes in patient's medical history **AND**
  - Two ECGs (from any forms of rhythm monitoring) showing continuous AF with ECGs taken at least 7 days apart, within last 12 months. **OR**
  - History of failed DC cardioversion (electrical or pharmacologic)

It is anticipated that the data from this randomized pivotal clinical study will be used to support a premarket approval application (PMA) to obtain Food and Drug Administration (FDA) approval to market the EPi-Sense®-AF Guided Coagulation System with VisiTrax® for the treatment of symptomatic persistent AF in patients who are refractory or intolerant to at least one Class I and/or III AAD.

1.2 Name and Intended Use of Device

Common Name:	Surgical Device for Ablation of Cardiac Tissue
Trade Name:	EPi-Sense®-AF Guided Coagulation System with VisiTrax®
Intended Use:	The EPi-Sense-AF Guided Coagulation System with VisiTrax is intended for the treatment of symptomatic persistent Atrial Fibrillation that is refractory or intolerant to at least one Class I and/or III anti-arrhythmic drug (AAD) when used with an open irrigated RF ablation catheter to complete PV isolation by ablating breakthroughs between the epicardial lesions.

1.3 Study Design

This is a, prospective, open label 2:1 randomized (convergent procedure versus standalone endocardial catheter ablation) multi-center pivotal clinical study. The study will enroll and randomize one hundred and fifty three (153) patients from up to thirty (30) sites, twenty-seven (27) US and three (3) OUS.

Potential subjects with symptomatic persistent AF will be screened by the sites for study participation. Consented subjects meeting all inclusion / exclusion criteria will be enrolled and randomized into the study.

Subjects in both arms of the study will be evaluated post procedure at 1 month, 3 months, 6 months and 12 months with a long-term follow-up visit at 18 months and long-term phone follow-up at 2, 3, 4, 5 years as detailed in this protocol. Submission for premarket approval will be filed after study subjects in both arms of the study complete the one year post procedure follow-up visit.

Annual reports will be submitted to the Agency in compliance with FDA regulatory requirements. One month safety data for the first 50 subjects in the treatment arm will be submitted to the FDA for review. During the conduct of this randomized study, any reported death, pericardial effusion leading to therapeutic drainage, atrio-aesophageal fistula or stroke will be reported to the Agency within 10 days.

1.4 Study Objectives

The objective of this clinical study is to evaluate the safety and efficacy of the EPi-Sense-AF Guided Coagulation System with VisiTrax for the treatment of symptomatic persistent AF as compared to a standalone endocardial catheter ablation.

1.4.1 Primary Objectives

To demonstrate superiority of the convergent procedure (experimental) compared to the standalone endocardial catheter ablation (control) on overall success, defined as freedom from AF/AFL/AT absent class I and III AADs except for a previously failed class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post procedure follow-up visit.

The incidence rate of Major Adverse Events (MAEs) in the treatment arm will demonstrate an acceptable risk profile.

1.4.2 Secondary Objectives

To demonstrate the efficacy of the procedure as a 90% reduction in the subject's baseline AF burden at 12 months post procedure in the presence or absence of class I / III AADs and a change in QOL measures and the six minute walk test scores from the baseline to 12 months post procedure.

1.4.3 Exploratory Objectives

To demonstrate the efficacy of the procedure as a 90% reduction in the subject's baseline AF burden at 18 months post-procedure in presence or absence of Class I/III AAD's.

To explore the impact of the convergent procedure on left atrial size and left ventricular ejection fraction. In addition we may evaluate the number of hospitalizations, total number of days hospitalized, and number of rhythm disturbance treatments for a period of 12 months before and after the convergent procedure for a health economics data analysis.

1.5 Study Endpoints

1.5.1 Primary Efficacy Endpoints

The primary efficacy endpoint is success or failure to be AF/AT/AFL free absent class I and III AADs except for a previously failed or intolerant class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post procedure follow-up visit.

The results of the holter data used for the primary efficacy endpoint evaluation will be evaluated by an independent reviewer thus maintaining the objectivity of the primary efficacy endpoint.

Subjects will be considered primary efficacy failures if any of the following conditions are observed:

- Any electrocadiographically documented AF/AFL/AT episode of 30 sec duration or longer by Holter, event monitor or rhythm strip; or for the full 10 second recording of a standard 12 lead ECG following the 3 month blanking period through the 12 months post procedure follow-up visit.
- The use of a new or an increase in the dose of a previously failed class I or class III AAD following the 3 month blanking period through the 12 months post procedure follow-up visit.
- DC cardioversion for AF/AFL/AT following the 3 month blanking period through the 12 months post procedure follow-up visit.
- Subsequent left-sided catheter ablation for AF/AFL/AT at anytime during the 12 months post procedure follow-up visit.
- Catheter ablation for right-sided typical atrial flutter following the 3 month blanking period through the 12 months post procedure follow-up visit.

1.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Success or failure to achieve a 90% reduction from baseline AF burden and off all Class I and III AADs at 12 months post procedure
- Success or failure to achieve a 90% reduction from baseline AF burden regardless of their Class I and III AAD status at 12 months post procedure
- Change in QOL measures at 12 months post procedure from baseline values
- Change in 6 minute walk test score from baseline score
- Success or failure to be AF free and off all Class I and III AADs except a previously failed or intolerant Class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post procedure follow-up visit
- Success or failure to be AF free regardless of Class I and III AAD status following the 3 month blanking period through the 12 months post procedure follow-up visit.

1.5.3 Primary Safety Endpoint

The primary safety endpoint for the study will be defined as the incidence of major adverse events (MAEs) listed below for subjects undergoing the convergent procedure for the procedural to 30 day post procedure time period.

All MAEs will be adjudicated by the Clinical Events Committee (CEC), thus maintaining the objectivity of the primary safety endpoint.

- Cardiac tamponade/perforation: is defined as the development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, and results in a 1 cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade/perforation should also be classified as “early” or “late” depending on whether it is diagnosed during or following initial discharge from the hospital.
  Documentation of CT Scan/MRI/ECHO findings and subsequent treatment such as thoracentesis or pericardiocentesis.
- Severe Pulmonary vein (PV) stenosis: Narrowing of the pulmonary veins. PV stenosis can be categorized as mild (<50%), moderate (50–70%), and severe (≥70%) reduction in the diameter of the PV or PV branch. Severe PV stenosis should be considered a major complication of AF ablation.
  Documentation by CT or MRI scan of ≥70% vessel narrowing compared to the baseline.
- Excessive Bleeding: is defined as a major complication if it is subsequent to a device related or study procedure-related injury and is treated with transfusion or results in a 20% or greater fall in HCT. Transfusion for anemia or other pre-existing conditions

that cause a fall in HCT without acute bleeding will not be considered a Major Adverse Event.
Documentation of the cause of the bleed, and transfusion, and/or 20% or greater drop in HCT.

- Myocardial infarction (MI): When low blood flow causes the heart to starve for oxygen. Heart muscle dies or becomes permanently damaged.
  Documentation of 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 1 h, (2) development of new pathological Q waves on an ECG, and (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Stroke: A stroke is an interruption of the blood supply to any part of the brain. Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.
  Duration of a focal or global neurological deficit ≥24 h; OR <24 h if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death AND no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences).
  Diagnosis should be confirmed by a neurology or neurosurgical specialist utilizing a neuroimaging procedure (MR or CT scan or cerebral angiography) or lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage).
  Documentation of a stroke or CVA consisting of acute loss of neurological function caused by an ischemic event with residual symptoms at least 24 hours after onset confirmed by CT or MRI scan or cerebral angiography of acute neurological event.
- Transient Ischemic attacks (TIA): A transient ischemic attack is a "mini-stroke" caused by Temporary disturbance of blood supply to an area of the brain, which results in a sudden, brief decrease in brain function. Clinical symptoms similar to stroke but last for less than 24 hours.
  Documentation of TIA neuroimaging without tissue injury consistent with acute loss of neurological function caused by an ischemic event with resolution of symptoms within 24 hours after onset.
- Atrioesophageal fistula: An atrioesophageal fistula is defined as a connection between the atrium and the lumen of the esophagus.
  Documentation of an atrial–esophageal fistula: A CT or MRI scan and 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.
- Phrenic Nerve Injury: Injury to the phrenic nerve that may be caused during the surgical procedure to access the heart or during ablation (epicardial or endocardial).
  Documentation of clinical signs or symptoms for phrenic nerve injury such as paralysis of the diaphragm on one or more sides confirmed by fluoroscopy or a chest X-ray.
- Death: Document cause of death and include autopsy findings if autopsy performed.

1.5.4 Secondary Safety Endpoint

The secondary safety endpoint for the study will be the incidence of serious adverse events (SAEs) in the study through the 12 month post procedure visit, in each arm of the study.

1.5.5 Exploratory Endpoints

- Success or failure to achieve a 90% reduction from baseline AF burden with and without Class I and III AADs at 18 months post procedure
- Change in left ventricular ejection fraction
- Atrial remodeling assessed by a decrease in left atrial size

- Health Economics Data
    - Change in number of hospitalizations and total number of days hospitalized for the 12 months (6 months to 18 months post procedure) post procedure period compared to hospitalizations 12 months prior to the procedure
    - Change in rhythm disturbance treatments (e.g. electrical or pharmacological cardioversion, AAD therapy, supraventricular ablative therapy) 12 months (6 months to 18 months post procedure) post procedure period compared to 12 months prior to the procedure

1.6 Duration of Investigation

Based on an enrollment of 153 randomized persistent AF subjects, it is anticipated that all subjects will be enrolled within 36 months after study initiation. The study will end when the last enrolled subject completes the 12 month post-procedure follow-up visit. Therefore, study duration is anticipated to be approximately 48 months.

2.0 DEVICE DESCRIPTION

2.1 EPi-Sense®-AF Guided Coagulation System with VisiTrax® Overview

The fourth generation coagulation device, EPi-Sense Guided Coagulation System with VisiTrax®, has been cleared for the endoscopic coagulation of cardiac tissue (510k K120857, K142084). The subject device for this study will be labeled EPi-Sense®-AF Guided Coagulation System with VisiTrax® *For Investigational Use Only*.

The device consists of a flexible radiofrequency coil electrode assembly that can be applied consistently to the epicardial surface of cardiac tissue by vacuum (designed to eliminate gaps along the lesion), a perfusion component designed to keep the tissue surface hydrated and the device surfaces not contacting cardiac tissue cool throughout the coagulation process, and sensing electrodes between select coil electrode windings to transmit cardiac electrograms to an external EP Recording System and transmit pacing pulses from an external stimulator; the complete Coagulation System also includes a customized RF generator that transmits energy to the device, and accessory cables to connect the coagulation device to the RF generator and route sensing electrode signals to an external EP Recording System. The Cannula Accessory is also provided to facilitate access for operative and diagnostic instrumentation including the EPi-Sense-AF Guided Coagulation device with VisiTrax, and enable endoscopic visualization throughout the lesion creation procedure.

The EPi-Sense-AF Guided Coagulation System with VisiTrax has been designed to provide the following benefits:

- Consistent contact with epicardial cardiac tissue regardless of cardiac anatomy
- Precise lesion creation without damage to surrounding tissue
- Continuous and complete lesions
- Visible lesions to interconnect into a pattern
- Device maneuverability to perform the coagulation of cardiac tissue under direct endoscopic visualization without chest incisions or lung deflation
- Use of temporary cardiac signal sensing to confirm device location.

The EPi-Sense-AF Guided Coagulation System with VisiTrax is able to coagulate cardiac tissue from the epicardial surface. The ability to coagulate tissue epicardially allows the procedure to be performed on a beating heart. The ability to access the posterior epicardium allows the procedure to be performed endoscopically without chest incisions, lung deflation, or dissections of the pericardial reflections (attachments between the pericardium and atrium).

The Operator's Manual for the RF Generator and the Instructions for Use for the EPi-Sense-AF Guided Coagulation System with VisiTrax and the Cannula Accessory must be reviewed prior to system use.

3.0 BACKGROUND

3.1 Atrial Fibrillation

AF is characterized by very fast, irregular beating of the heart's upper chambers (the atria). It occurs when normal sinus rhythm is disrupted by errant irregular electrical signals in the atria. These erratic electrical propagation patterns disrupt the regular pumping action of the atria, preventing complete filling of the ventricles, and causing irregular beating of the ventricles. These spasms often lead to regions of static blood flow in the atria and consequently, blood clot formation, stroke and even death. It is estimated that AF is responsible for 15% - 25% of all strokes. Symptoms of AF typically include a rapid and irregular heartbeat, palpitations, dyspnea, discomfort, dizziness and fatigue.

Atrial fibrillation (AF) is a common heart arrhythmia that carries a significant mortality and morbidity risk, and is associated with three primary clinical sequelae: loss of atrial transport, loss of regular cardiac chamber synchronization, rhythm & rate response, and thromboembolism. Up to a third of all patients with persistent AF will experience at least one embolic episode during the course of their atrial fibrillation. Lone AF (e.g. no structural heart disease) with no left atrial enlargement may be categorized as a benign disease since it is not associated with an increase in mortality or complications than that of the general population. However, AF patients, especially those with enlarged atria or structural heart disease, are at an increased risk of congestive heart failure, thromboembolic events, and mortality.[i] In fact, permanent AF (longstanding persistent AF after the decision not to treat) is associated with 8.2% annual all-cause mortality, 5.1% annual thormboembolic event rate, 2.7% annual major bleeding rate, and 16.6% annual heart failure rate.[ii]

The underlying theory surrounding the source of irregular conduction pathways in patients with atrial fibrillation involves ectopic electrical activity or micro-reentrant circuits that can originate from specific locations in the heart such as the pulmonary vein orifice in patients with lone AF (focal), or more commonly associated with the reentry of conduction circuits throughout the atria in patients with structural remodeling (wavelet AF).

Only 12% of patients have Lone AF, leaving the remaining 88% with some form of structural heart disease.[iii] This structural heart disease commonly includes hypertension, coronary artery and valvular heart disease. Left untreated, AF can lead to ventricular dysfunction, atrial dysfunction, left atrial enlargement thus perpetuating the structural remodeling that causes and worsens atrial fibrillation and heart failure.[iv]

The relationship between progressive structural remodeling and atrial fibrillation explains why 88% of AF patients are persistent or permanent leaving only 12% as paroxysmal.[v] Furthermore, 76% of AF patients either have enlarged atria with diameter greater than 4.5 cm or an increase in left ventricular thickness.[vi] Atrial enlargement, as well as structural remodeling, determines the incidence of atrial fibrillation and whether AF patients observe complications throughout their lifetime.

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[i] Osranek M. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up . European Heart Journal (2005) 26, 2556–2561.
[ii] Nieuwlaat R, et al. Prognosis, disease progression, and treatment of atrial fibrillation during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. Eur Heart J. 2008;29:1181-1189.
[iii] Fuster and Rydén et al. ACC/AHA/ESC Practice Guidelines. JACC Vol. 38, No. 4, October, 2001.
[iv] Ommen SR, et al. Usefulness of serial echocardiographic parameters for predicting the subsequent Thisoccurrence of atrial fibrillation. Am J Card. Vol 87. June 1, 2001.
[v] Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Arch Intern Med 1994;154:1449-1457.
[vi] Pritchett A. et al. Left Atrial Volume as an Index of Left Atrial Size: A Population-Based Study. J Am Coll Cardiol 2003;41:1036–43.

Patients newly diagnosed with AF are medically managed with multiple courses of antiarrhythmic drugs (AAD), and anticoagulants to lessen the risk of thromboembolic accidents. Within 5 years, most patients will become refractory to AADs, and will require additional intervention. Often AADs will have the effect of "dumbing down" the heart's natural pacemaker, necessitating the need for permanent rate control. Although the risk of thromboembolism is reduced in the presence of anticoagulation, it is still substantially higher than that observed in the general population. In addition, bleeding complications from anticoagulation regimens occur at a cumulative rate of 1% per year.

3.2 Atrial Fibrillation Classification

The HRS/EHRA/ECAS (2012) Guidelines have classified AF into 3 groups.[vii]

- Paroxysmal AF is defined as recurrent AF (>2 episodes) that terminates spontaneously within seven days.
- Persistent AF is defined as AF which is sustained beyond 7 days. Episodes of AF which are terminated by electrical or pharmacologic cardioversion after $\geq$ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
- Longstanding persistent AF is defined as continuous AF greater than one-year duration.

The term permanent AF is not appropriate in the context of patients undergoing ablation of AF as it refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation.

3.3 Treatment of Atrial Fibrillation

As described in 3.1, AF is typically first treated with drug therapy, with an approximately equal split between rate and rhythm control drugs as first line of treatment. Recent large scale studies have failed to show superiority of one treatment approach - rate or rhythm control - over another. Regardless of rate or rhythm control, continuous anticoagulation therapy is crucial in AF patients for stroke prevention. The AFFIRM study concluded that the benefit of restoring sinus rhythm in the rhythm control group was reversed by the toxicity of the antiarrhythmic drugs and hypothesized that if a treatment was available to restore sinus rhythm without the toxicity of antiarrhythmic drugs, survival may be improved.

Drug therapy failure may be due to either a lack of medication efficacy and/or a patient's inability to tolerate medications known to have serious and bothersome side effects, including those resulting from interactions with other drugs. According to its package insert, Cardarone® (amiodarone), the most widely-prescribed anti-arrhythmic medication (not approved for the treatment of AF), is discontinued in 7-18% of patients due to intolerable side effects.

Surgical treatment of AF is usually considered when a patient is already scheduled for a concomitant cardiac procedure requiring access to the thoracic cavity. When performed concomitantly, the surgical treatment of AF is often performed using cardiopulmonary bypass on an open and arrested heart. The surgeon is unable to observe atrial function and cannot confirm treatment success intraoperatively because the atria must be beating in order to place a pacing electrode and confirm conduction block.

The Maze procedures (and its derivatives, Maze III, etc.), are considered the comparative standard for the effective treatment of AF. The Maze III procedure requires stopping the heart and then surgically cutting and re-sewing the atria to create a complex pattern of lesions throughout the atria that are intended to block macro-reentry circuits within the atria. In the intervening years, the Maze III procedure has been modified, but it remains the standard for

[vii] 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. J Interv Card Electrophysiol. 2012;33(2):171-257.

treatment of atrial fibrillation. However, associated procedural mortality (2 to 10%) and morbidity including permanent pacemaker requirements (~15% of patients) have hindered the adoption of “cut and sew” procedure.

There have been many attempts to move away from the complexity and risk of the cut and sew Maze III procedure. Most of the effort has focused on procedures to isolate errant conduction signals that are suspected to originate from the pulmonary veins either by segmental ostial ablation or by the creation of a box lesion around the pulmonary veins. Electrically isolating the pulmonary veins may be effective for focal AF patients who have paroxysmal AF with no structural heart disease. However, more complex types of AF require a more comprehensive lesion pattern to block all reentrant circuits, and therefore sole isolation of the pulmonary veins is not an effective treatment.

To date, a percutaneous catheter-based or minimally invasive surgical procedure that can effectively and safely treat persistent or longstanding persistent Atrial Fibrillation (AF) is unavailable.

The ideal treatment for AF would mitigate the detrimental sequelae of AF; that is, the procedure would restore normal sinus rhythm and cardiac hemodynamics, prevent continued remodeling and enlargement of the atria, and reduce the risk of thromboembolism. The ideal procedure would provide a means for assessing completeness of the lesion patterns. Continuous and complete lesions created throughout the atria and electrically silencing the posterior left atrium as well as isolating the pulmonary veins are most likely to prevent propagation of electrical signals capable of inducing and/or maintaining AF, and prevent development of new reentrant circuits or atrial enlargement. The ideal procedure would also be performed utilizing minimally invasive, closed chest techniques.

AtriCure has developed a cardiac tissue coagulation system that may provide improved performance over current treatment options. Atricure’s technology is based on a low profile, flexible radiofrequency (RF) coagulation device that provides consistent contact with the tissue through the use of vacuum. The technology ensures reliable contact, conformation to any tissue region of the heart, as well as localized-directional treatment to make conventional cardiac tissue coagulation more predictable. The system also incorporates a perfusion lumen coupled to the vacuum source that 1) hydrates tissue that is in contact with the device electrode, and 2) cools the non-tissue contacting surfaces of the device. The vacuum perfused device design controls energy delivery, minimizes the risk of over-heating tissue that is being coagulated and thus, the risk of charring and tissue vaporization, and also prevents damage to non-targeted, adjacent tissues and anatomical structures.

The inclusion of sensing electrodes to the coagulation device has provided additional input to the operator as to the type of tissue targeted for ablation and evaluation of the extent of ablation. Electrograms, recorded from tissue against which the coagulation electrode contacts, augment the direct endoscopic visualization of electrode position by determining definitively that the sensing electrodes, thus the coagulation electrode, contact target atrial tissue. The sensing electrodes provide input throughout energy delivery on the extent and completeness of cardiac coagulation by delineating electrically viable tissue from non-viable tissue which coincides with a substantial reduction in cardiac electrogram amplitude. In addition, the sensing electrodes allow transmission of pacing stimuli to tissue for evaluating the isolation of the posterior left atrium and pulmonary vein isolation at locations accessible from a transdiaphragmatic or sub-xyphoid pericardial window.

AtriCure has taken the coagulation of cardiac tissue one step further with the Guided Coagulation System that allows the procedure to be performed without the need for chest incisions. The use of a cannula facilitates access and provides visibility to the posterior surface of the heart allowing the creation of lesions on the epicardium of the atria under direct visualization.

The one limitation, which ends up being a substantial benefit, of the closed chest, transdiaphragmatic or sub-xyphoid access is the inability to dissect the pericardial reflections (attachments between the atria and pericardium). This reduces the perforation risks since those dissections are adjacent to thin, fragile tissue but hinders the ability to create lesions completely around the pulmonary veins. The reflections are short, and are located above the right and left superior pulmonary veins and below the right inferior pulmonary vein. To address this limitation, AtriCure has proposed treatment for persistent AF that incorporates endocardial catheter ablation to complete pulmonary vein isolation by ablating known breakthrough locations in the epicardial linear lesions at the pericardial reflections, and ablate the cavotricuspid isthmus to prevent typical AFL. This multidisciplinary approach combines epicardial and endocardial ablation procedures into a truly minimally invasive approach that does not require chest incisions or lung deflation. AtriCure is proposing this randomized pivotal study to evaluate the safety and efficacy of the EPi-Sense-AF Guided Coagulation System with VisiTrax for the treatment of symptomatic persistent AF. The premise of this Convergent Procedure stems from the complementary nature of both approaches.

4.0 SUBJECT SELECTION AND ENROLLMENT PROCEDURES

4.1 Study Population

All subjects enrolled in the study will be recruited from the pool of subjects presenting for the treatment of symptomatic persistent AF.

All subjects will be male or female older than eighteen (18) years and younger than eighty (80) years.

4.2 Inclusion Criteria

All subjects recruited for study participation must meet all of the following inclusion criteria to be enrolled in the study:

- Age > 18 years; < 80 years
- Left atrium $\leq$ 6.0 cm (Trans Thoracic Echo - TTE – parasternal 4 chamber view)
- Refractory or intolerant to one AAD (class I and/or III)
- Documentation of persistent AF
- Provided written informed consent

4.3 Exclusion Criteria

Potential subjects recruited for study participation must not meet any of the following exclusion criteria to be enrolled in the study:

- Patients requiring concomitant surgery such as valvular repair or replacement, coronary artery bypass graft (CABG) surgery and atrial septal defect closure.
- Left ventricular ejection fraction < 40%
- Pregnant or planning to become pregnant during study
- Co-morbid medical conditions that limit one year life expectancy
- Previous cardiac surgery
- History of pericarditis
- Previous cerebrovascular accident (CVA), excluding fully resolved TIA
- Patients who have active infection or sepsis
- Patients with esophageal ulcers strictures and varices
- Patients with renal dysfunction who are not on dialysis (defined as GFR ≤ 40)
- Patients who are contraindicated for anticoagulants such as heparin and coumadin
- Patients who are being treated for ventricular arrhythmias
- Patients who have had a previous left atrial catheter ablation for AF (does not include ablation for AFL or other supraventricular arrhythmias)
- Patients with existing ICDs.

- Current participation in another clinical investigation of a medical device or a drug, or recent participation in such a study within 30 days prior to study enrollment
- Not competent to legally represent him or herself (e.g., requires a guardian or caretaker as a legal representative).

4.4 Informed Consent

All subjects recruited for study participation must meet all study enrollment inclusion / exclusion criteria prior to being enrolled / randomized in the study. Once compliance with study inclusion/exclusion criteria is confirmed, and the Investigator has determined that a subject is potentially eligible for study participation, the subject may be asked to participate in the study. Informed consent must be obtained from all study subjects prior to study participation and initiation of any study-related procedures. A template informed consent will be provided to the sites.

All participating Investigational Sites will provide the sponsor (AtriCure) with a copy of the Informed Consent approved by the Institutional Review Board (IRB)/Ethics Committee (EC) overseeing the conduct of this study for that site. The original signed informed consent will be retained in the study subject's study records and a copy of the consent should be provided to the subject.

Once study eligibility is confirmed and subject enrolled, a study subject ID will be assigned to each subject. Subject ID will be a 3 digit number assigned to the site followed by a 3-digit subject number starting with 101 and ascending chronologically. All data will be entered into the electronic data capture system developed for the study.

4.5 Study Eligibility and Baseline Assessments

All subjects recruited for study enrollment must meet all study enrollment criteria described in 4.2 – 4.4 prior to being enrolled in the study. Once the initial chart review indicates that the subject meets the study inclusion / exclusion criteria and the subject has agreed to study participation and signed the informed consent, the following baseline assessments will be completed to further determine study procedure eligibility. Baseline evaluations must be completed within 90 days of the procedure. The patient will be considered enrolled in the study once the consent has been signed.

- Demographic information
- Medical history
- Cardiac history
- Documentation of persistent AF
    - Physician notes in patient's medical history **AND**
    - Two ECGs (from any forms of rhythm monitoring) showing continuous AF with ECGs taken at least 7 days apart, within last 12 months **OR**
    - History of failed DC cardioversion (electrical or pharmacologic)
- Twenty four hour continuous holter monitor
- ECHO (TTE – 4 chamber parasternal view) to include
    - Atrial size (left atrium diameter)
    - Left ventricular ejection fraction (LVEF)
    - Presence/absence of thrombi in left atrium (If thrombus present patient is excluded from study).
- Spiral CT scan or MRI to evaluate baseline pulmonary vein stenosis and atrial volume
- Medications history – Antiarrhythmic drugs (AADs), cardiac medications and anticoagulants including previous AAD treatment failures. Medication information should include
    - Name and indication
    - Dosage with units and frequency
    - Start and stop dates
- Six minute walk test

- Quality of Life (QOL) assessments (SF36, University of Toronto)
- TEE performed immediately pre-procedure.
- Hospitalizations and rhythm disturbance treatments 12 months prior to procedure.

The study eligibility and baseline assessments data will be entered into the electronic data capture system developed for the study.

4.6 Subject Randomization

Subjects who have consented to study participation, have met all inclusion/exclusion criteria and have completed all baseline evaluation and are eligible for study participation will be randomized to either the convergent procedure or standalone endocardial catheter ablation procedure.

Randomization will be implemented using Tempo™, the electronic research tool used for collecting clinical data. Randomization will be blocked by investigator site on randomly chosen blocks of 3 or 6 patients allocated 2:1 to the treatment arms, respectively. Appropriate randomization codes will be provided on the screen immediately after randomization for a subject is requested. The treatment arm code will be automatically stored in the study database.

Subjects becoming ineligible for the convergent or the endocardial catheter ablation procedure as a result of meeting the study intra-op exclusion criteria will be replaced.

5.0 STUDY PROCEDURE

Subject preparation for the convergent procedure or the standalone endocardial catheter ablation procedure will follow the Investigator's and study site's standard of practice pre-operative and pre-catheterization patient care instructions.

5.1 Procedure Intra-Op Exclusions

Prior to initiating the study convergent procedure or the standalone endocardial catheter ablation procedure, review subject anatomy and TEE or ICE results to confirm that the subject does not meet any of the study intra-op exclusions listed below:

- Presence of left atrial thrombi per immediate pre-op Trans-Esophageal Echocardiograph (TEE) for the convergent procedure, and per TEE or Intra cardiac Echo (ICE) for the standalone endocardial catheter ablation procedure.
- Presence of adhesions that would prevent epicardial access to the pericardial space or the creation of the study recommended complete lesion pattern. (Convergent procedure arm only)

If the subject meets any of the above intra-op exclusions, the study procedures will not be performed. Subjects meeting the intra-op exclusions will be followed for 30 days post procedure and will be included in the study safety analysis only. Alternative treatment procedures for the subject's AF should be scheduled after the subject's 30 day follow-up for safety and study participation is completed.

5.2 Study Procedure – Convergent Procedure Arm

Once the procedure intra-op exclusion conditions have been evaluated, the epicardial lesion pattern will be created using the EPi-Sense-AF Guided Coagulation System with VisiTrax. The recommended study procedure outlined in Attachment A, and the Investigator's Training Guide should be followed to create the epicardial / endocardial lesion pattern.

Epicardial linear lesions will be created endoscopically using the EPi-Sense-AF Guided Coagulation System with VisiTrax throughout the posterior left atrium and along the pericardial reflections from a trans-diaphragmatic or sub-xyphoid access without any chest incisions. The

pericardial reflections will not be dissected. An endocardial ablation catheter will be used to ablate endocardially to connect lesions at the reflections to complete the isolation of the pulmonary veins, and create a cavotricuspid lesion to prevent typical atrial flutter. For patients with inducible atrial arrhythmias (atypical atrial flutter, atrial tachycardia, AVNRT, etc.) the arrhythmia may be mapped and ablated. If the subject does not organize into AT or SR, then the patient should be cardioverted through the administration of Ibutilide or electrical cardioversion. Posterior and other linear lesions such as a roof lesion and mitral valve isthmus lesion will not be created during the endocardial component of the convergent procedure.

Once the study lesion pattern has been created by coagulating cardiac tissue using the EPi-Sense-AF Guided Coagulation System and the endocardial ablation catheter, the pulmonary veins must be evaluated for entrance and/or exit block to confirm isolation. Follow the protocol provided in Attachment C to confirm pulmonary vein isolation.

The following procedure and post procedure data will be entered into the electronic data capture system developed for the study.

- TEE - Presence /absence of thrombi in LA
- Physicians performing the procedure
- Total Convergent procedure time
  (Abdominal incision to removal of catheters-not sheath pull)
- Total epicardial procedure time
  (Abdominal incision to abdominal access site closure)
- Total time to create the epicardial component of the lesion pattern
  (Total epicardial ablation procedure time = time from first lesion to last lesion)
- Epicardial system generator power setting
- Number of RF applications for EPi-Sense-AF Guided Coagulation system
- Max Power setting for the endocardial lesions
- Total endocardial procedure time
  (Groin access to removal of catheters)
- Total time to create endocardial lesion pattern
  (Time from first lesion to last lesion)
- Total time for left atrial lesions
- Total time for right atrial lesions
- Total endocardial RF ablation time
  (Cumulative time of RF energy delivery)
- Total Fluoro time
- Total Fluoro time for left atrial ablation
- Total Fluoro time for right atrial ablation
- Exit and /or entrance block tested on the pulmonary veins
- Exit and /or entrance block confirmation for the pulmonary veins
- Rhythm observed after Endocardial ablation procedure on leaving the procedure room
- Adverse event assessment
- Lot number and expiration date for epicardial and endocardial devices used to create the study lesion pattern
- Any epicardial or endocardial device malfunction
- Cardiac medications and anticoagulants administered during the procedure

Total epicardial ablation procedure time to create the lesion pattern using the EPi-Sense-AF Guided Coagulation System with VisiTrax should take approximately 1 to 2 hours. Total endocardial ablation procedure should take 2 to 4 hours. Total Convergent procedure time should take approximately 4-6 hours

The Instructions for Use included with the RF generator, EPi-Sense-AF Guided Coagulation System, accessories, and endocardial ablation system should be reviewed for additional directions for use and troubleshooting tips.

5.3 Study Procedure – Standalone Endocardial Catheter Ablation Arm

The Endocardial lesion pattern will be created using one of the irrigated endocardial catheter listed in Attachment B. To create the endocardial lesion pattern, follow the suggested lesion creation steps described in Attachment B. Access the anatomical locations endocardially, and create the lesion pattern which includes isolating the left and right pulmonary veins, connecting the PV isolation lesions with an atrial roof lesion, and ensuring bidirectional block across a cavotricuspid isthmus lesion. The electrophysiologist can spend up to 30 min in the control arm doing CFAE ablation (must not be making linear lesions) if, after PVI and the roof lesions, the patient's rhythm does not organize into an atrial flutter (AFL) or atrial tachycardia (AT) or convert to sinus rhythm; CFAE is defined as constant electrical activity or local activity with an atrial electrogram cycle length <120 msec.[viii,ix] For patients that convert to an AT or AFL or develop inducible atrial arrhythmias (AFL, AT, AVNRT, etc.) the arrhythmia may be mapped and ablated. If the subject does not organize into AFL, AT, or SR then the patient should be cardioverted through the administration of Ibutilide or electrical cardioversion. The completion of each lesion may require multiple sequential placements. If additional lesion(s) are created or suggested lesions are not created, this must be entered into the electronic data capture system developed for the study.

Once the study lesion pattern has been created using the endocardial ablation catheter, the pulmonary veins must be evaluated for entrance and/or exit block to confirm isolation. Follow the pacing protocol provided in Attachment C to confirm pulmonary vein isolation.

The following procedure and post procedure data will be entered into the electronic data capture system developed for the study.

- ICE/TEE - Presence /absence of thrombi in LA
- Max Power setting for the endocardial lesions
- Total endocardial procedure time
  (Groin access to removal of catheters)
- Total time to create endocardial lesion pattern
  (Time from first lesion to last lesion)
- Total time for left atrial lesions
- Total time for right atrial lesions
- Total endocardial RF ablation time
  (Cumulative time of RF energy delivery)
- Total Fluoro time
- Total Fluoro time for left atrial ablation
- Total Fluoro time for right atrial ablation
- Exit and /or entrance block tested on the pulmonary veins
- Exit and /or entrance block confirmation for the pulmonary veins
- Rhythm observed on leaving the EP lab
- Adverse event assessment
- Lot number and expiration date for endocardial devices used to create the study lesion pattern
- Any endocardial device malfunction

[viii] Knecht S, et al. Impact of pharmacological autonomic blockade on complex fractionated atrial electrograms. J Cardiovasc Electrophysiol. 2010;21(7):766-702.
[ix] Oral H, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol. 2009;53:782-9.

- Cardiac medications and anticoagulants administered during the procedure

Total endocardial ablation procedure time to create the lesion pattern should take approximately 4 hours. The manufacturer's Instructions for Use included with the RF generator, and endocardial ablation system should be reviewed for additional directions for use and troubleshooting tips.

5.4 Acute Procedural Success

Acute procedural success will be assessed as the completion of the study defined lesion pattern and pulmonary vein isolation as demonstrated by entrance and /or exit block.

6.0 POST PROCEDURE FOLLOW-UP ASSESSMENTS

All study subjects in both arms of the study will be followed at 7 days, 1 month, 3 months, 6 months, and 12 months with a long-term follow-up visit at 18 months and long-term phone follow-up at 2, 3, 4, 5 years post index procedure as detailed in this protocol. The follow-up assessment data will be entered into the electronic data capture system developed for the study.

Subjects should be weaned off any Class I and III AADs at the 3 month post procedure visit unless medically indicated (alternatively, subjects may continue previously failed class I or III AAD at the previous dose or lower). All cardiac medications will be prescribed as medically indicated or per physician standard of practice.

All Holter monitor recordings will be reviewed by an independent reviewer designated by the Sponsor: AtriCure.

6.1 Blanking Period

The period from index procedure to the 3 month post procedure visit will be considered a blanking period. During the blanking period, the use of AADs, cardioversions, and any recurrence or episodes of AF will not be considered a treatment failure. Subjects who receive AF therapy (a new class I/III AAD, or an increase in dose of a previously failed class I/III AAD therapy, DCCV, pharmacological cardioversion, RFCA) following the 3 month blanking period through the 12 months post procedure follow-up visit will be considered primary efficacy failures. Subjects receiving RFCA for the treatment of AF, left-sided atypical atrial flutter, or atrial tachycardia at anytime (even within the blanking period) after the index procedure will be deemed primary efficacy failures; any RFCA should be performed in accordance with Attachment F – Repeat Catheter Ablation Protocol. Subjects in either arm of the study who are efficacy failures (documented by the 24 hour holter results), at the six month post procedure follow-up time point, may undergo an ablation procedure per physician recommendation. Subjects will be deemed efficacy failures, the ablation will be recorded as a rhythm disturbance treatment within the TEMPO EDC system, and the subjects will be continued to be monitored per protocol requirements.

6.2 7 Day post procedure Visit (7 days +7 days post index procedure)

After completion of the study procedure subjects in both study arms will return for a post procedure follow-up visit at 7 days for an evaluation of any peri-procedural adverse symptoms. The 7 days post procedure evaluation will include:

- Evaluation of any adverse events
- Evaluation of any major adverse events (MAEs)
- Medications – Class I and III AADs, other cardiac medications and anticoagulants
- Trans Thoracic ECHO (TTE) to evaluate for any effusions
- Schedule subject for 1 month visit.

6.3 Month 1 visit (30 days + 7 days post index procedure)

After completion of the study procedure, the following assessments will be completed at 30 days post procedure:

- ECG – subject rhythm evaluation
- Evaluation of any adverse events
- Evaluation of any major adverse events (MAEs)
- Medications – Class I and III AADs, other cardiac medications and anticoagulants
- Any AF treatment that was needed
- Schedule subject for 3 month visit.

6.4 Month 3 Visit (90 days +/- 15 days post index procedure)

Subjects in both study arms will return for a post-procedure follow up visit at 3 months to evaluate their progress. The 3 month post procedure assessment will include:

- ECG – subject rhythm evaluation
- Evaluation of any adverse events
- Evaluation of any major adverse events (MAEs)
- Medications – Class I & III AADs, other cardiac medications and anticoagulants
- Subject should discontinue class I and III AADs if medically warranted (may alternatively continue previously failed class I or III AAD at pre-procedure dose or lower)
- Any AF treatment that was needed
- Schedule subject for 6 month visit with Holter monitor assessment
- Instruct subject to contact the site coordinator if they are experiencing any symptomatic atrial tachyarrhythmia episodes at anytime during the post 3 month blanking period/post-procedure follow-up visit through the 12 month post-procedure follow-up visit.

6.5 Month 6 Visit (180 days +/- 30 days post index procedure)

Subjects in both study arms will return for a post-procedure follow up visit at 6 months to evaluate their progress. The 6 month post procedure assessment will include:

- ECG – subject rhythm evaluation
- 24 hour Holter monitor
- ECHO (TTE – 4 chamber parasternal view) to include
    - Atrial size (left atrium diameter)
    - Left ventricular ejection fraction (LVEF)
    - Presence/absence of thrombi in left atrium.
- Evaluation of any adverse events
- Evaluation of any major adverse events (MAEs)
- Medications – Class I and III AADs, other cardiac medications and anticoagulants
- Any AF treatment that was needed
- Spiral CT or MRI to evaluate absence of PV stenosis and left atrial thrombus and atrial volume.
- Schedule subjects for 12 month visit with a 24 hour Holter monitor assessment

6.6 Month 12 Visit (365 days +/- 30 days post index procedure)

Subjects will return for a post-procedure follow up visit at 12 months to evaluate their progress. The 12 month post procedure assessment will include:

- ECG – subject rhythm evaluation
- 24 hour Holter monitor

- Evaluation of any adverse events
- Evaluation of any major adverse events (MAEs)
- Medications – class I and III AADs, other cardiac medications and anticoagulants
- Any AF treatment that was needed
- Quality of Life (QOL) assessments (SF36 and Univ. of Toronto)
- Six minute walk test
- Complete the subject study completion CRF
- Remind subject that he does have to come in for the long-term 18 month post procedure follow-up visit and participate in annual phone follow-ups at 2, 3, 4, 5 years post procedure.

6.7 Continued Long-term Follow-up

6.7.1 Month 18 Visit (550 +/- 30 days post index procedure)

Subjects in both study arms will return for a continued long-term post-procedure follow up visit at 18 months to evaluate their progress. The 18 month post procedure assessment will include:

- ECG – subject rhythm evaluation
- 7 Day Holter monitor
- Evaluation of any adverse events
- Evaluation of any major adverse events (MAE)
- Medications – class I and III AADs, other cardiac medications and anticoagulants
- Any AF treatment that was needed
- Hospitalizations and rhythm disturbance treatments following the 6 months post procedure follow-up to the 18 months post-procedure follow-up.

6.7.2 Annual Phone Follow-up at year 2, 3, 4 and 5 post procedure (+/- 30 days post index procedure)

The annual phone follow-up will be a health questionnaire answered over the phone. The questionnaire will include:

- Subject's current rhythm status
- Medications – class I and III AADs, other cardiac medications and anticoagulants
- Any AF treatment that was needed
- Evaluation of any adverse events
- Reminder of the next annual call.

6.8 Data Collection and Management

AtriCure or their designated CRO will be responsible for the design of the eCRF, monitoring the trial according to GCP guidelines, preparation of data queries and reports to assist the clinical monitoring, and training each study site staff member entering data in the eCRF. AtriCure or their designated CRO will also be responsible for preparation of analysis files from the database prior to analyses, assisting with the statistical analyses and statistical report, and preparation of the integrated clinical study report.

The electronic data capture (eDC) component of Tempo™ will be used for electronic data acquisition and storage. Tempo™ will provide electronic case report forms (eCRFs) for transfer of all research data by site personnel from data source documentation to the study database. Each responsible person at a site will have user access to Tempo™ through their unique username and password, with permissions providing each person their needed access. Some personnel will have data entry, data review, and query resolution permissions, while others may only have data read permissions, based on their individual study roles. Tempo™ is flexible to allow customizable permissions as needed for study personnel.

Study data will be checked for completeness and correctness as it is entered by the real-time online checks applied by Tempo™. Off-line checks will also be run to perform any additional

data review required. Any issues identified will be transferred to the study site via query for resolution by the investigator or his/her designee. All queries will be managed through Tempo™ and audit trails of all queries and their resolution, along with any data changes, will be recorded.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Clinical research associates (CRAs) will monitor the data, verifying captured data against its source. Monitoring will be enhanced by computer assisted data management identifying missing or possibly erroneous data as soon as data is entered into the system. This approach will allow initial remote monitoring, and communication between CRAs and site personnel before and between site visits, and will expedite data review and cleaning. Missing data and identified data errors (or possible errors) will be communicated by the CRAs to site investigators using the Query feature in Tempo™ for correction or acknowledgement that data is correct as entered. As each subject's data entry is completed and fully monitored with all queries resolved, that subject's data will be locked by the CRA to only allow read access for the remainder of the study.

Tempo™ and all study data are housed in a secure computing environment. Tempo™ further provides a complete audit trail of all data entry, monitoring, and query activity. Tempo™ is compliant with HIPPA and meets all requirements for 21 CFR Part 11.

Table 1: Study Data Collection Requirements

	Baseline	Pre-procedure	Procedure	7 Days	1 month	3 months	6 months	12 months
Informed Consent for Study Participation	✓							
Inclusion/Exclusion Criteria	✓	✓	✓					
Medical History	✓							
Spiral CT or MRI	✓						✓	
Procedure			✓					
ECG	✓		✓		✓	✓	✓	✓
ECHO (TTE)	✓			✓			✓	
ECHO (TEE)		✓						
24 hour Holter monitor	✓						✓	✓
Documentation of any AF treatments					✓	✓	✓	✓
Medication status Class I and III AADs, cardiac and Anticoagulants	✓		✓	✓	✓	✓	✓	✓
Evaluation of Adverse Events			✓	✓	✓	✓	✓	✓
Six minute walk test	✓							✓
Quality of Life Assessment (QOL)	✓							✓

Table 2: Continued Long Term Data Collection Requirements

	18 months	Phone F/U 2 years	Phone F/U 3 years	Phone F/U 4 years	Phone F/U 5 years
Health Status	✓	✓	✓	✓	✓
ECG	✓				
Rhythm status	✓	✓	✓	✓	✓
7 Day Holter monitor	✓				
Medications Class I and III AADs, cardiac and Anticoagulants	✓	✓	✓	✓	✓
Evaluation of Adverse Events	✓	✓	✓	✓	✓

7.0 INVESTIGATOR TRAINING

The investigators performing the epicardial ablation procedure portion of the study must be practicing cardio-thoracic surgeons. All study Investigators (whether they are performing the procedure or not) will be expected to complete Investigator training prior to participation in the study.

All investigators performing the endocardial ablation procedure for both arms of the study will be practicing electrophysiologists and will have documented training for the endocardial ablation catheters and equipment used at their site.

8.0 ADVERSE EVENTS

Safety data for the primary safety endpoint will be collected from the start of the coagulation procedure to 30 days post procedure. The primary safety endpoint will be an evaluation of the incidence of major adverse events (MAE) listed below for the procedural to 30 day post procedure time period, for each arm of the study.

The secondary safety endpoint for the study will be an analysis of the incidence of major adverse events, in each arm of the study, from 30 days post procedure through the 12 months post procedure visit, for each arm of the study.

8.1 Major Adverse Events (MAE)

Events qualifying as MAEs as defined in 1.5.4 include:

- Cardiac tamponade/perforation requiring pericardiocentesis or thoracentesis
- Severe Pulmonary Vein Stenosis (≥ 70% occlusion)
- Excessive bleeding requiring transfusion or > 20% drop in HCT.
- Myocardial infarction
- Stroke
- Transient Ischemic Attacks (TIA)
- Atrioesophageal fistula
- Phrenic nerve injury
- Death

Any condition that was recorded as pre-existing is not a MAE unless there is a change in the nature, severity or degree of the condition.

Sick Sinus Syndrome (SSS) and the implantation of a pacemaker for treatment of SSS post procedure will not be recorded as a MAE since it is a known underlying condition for patients with persistent AF and undergoing cardiac coagulation procedures.

8.2 Serious Adverse Events (SAE)

A serious adverse event by FDA definition is one that:

- Results in a fatality
- Is life-threatening
- Results in permanent disability
- Requires hospitalization or prolongs a hospital stay
- Requires medical or surgical intervention to prevent one of these outcomes.

Serious adverse events that are deemed device-related and/or procedure-related will be captured in the study.

8.3 Device Related Adverse Effects (DRAE)

An adverse event will be considered to be related to the device if it results from the use or presence of the device, or the performance of any component of the device. Device relatedness will be classified as either related or not related (for EPi-Sense-AF Guided Coagulation System).

8.4 Unanticipated Adverse Device Effects (UADE)

A device or procedure related adverse effect will be considered unanticipated if it is not identified in frequency, severity or nature in this protocol, or the EPi-Sense-AF Guided Coagulation System with VisiTrax Instructions for Use and the RF Generator operator's manual. Events that are deemed device-related and unanticipated are to be reported to AtriCure within 24 hours of the occurrence of the event, even if the event is not considered serious in nature.

8.5 Adverse Event Reporting

All DRAEs, and UADEs must be reported to AtriCure Surgical within 24 hours of the site becoming aware of them. All SAEs and MAEs must be reported to AtriCure within 7 days of the site becoming aware of them. The participating sites will be responsible for reporting, as required by their IRBs, any AEs, SAEs, DRAEs and UADEs to their local regulatory bodies.

Any death, pericardial effusion leading to therapeutic drainage, atrio-esophageal fistula or stroke will be reported to the FDA within 10 working days of AtriCure becoming aware of these complications.

One month safety data for the first 50 subjects in the treatment arm will be submitted to the FDA for review.

9.0 STATISTICAL ANALYSIS

9.1 Summary Descriptive Statistics

This randomized pivotal study plans to enroll 153 randomized subjects.

Standard descriptive statistics will be used to summarize numeric variables, including the number of observed values, mean, standard deviation, median, minimum and maximum values. Summaries of categorical variables will include the number and percentage of observed values, at each level of the categorical variable.

Baseline and demographic information, including age, gender, race, ethnicity, height, weight, BMI, and medical history will be summarized with standard descriptive statistics. Primary and secondary efficacy endpoints, including AF/AT/AFL free and Class I and III AAD status, 90% reduction in AF burden and Class I and III AAD status, and change in Quality of Life and 6 minute walk test scores will be summarized by visit. Categorical summaries will be based on the number of subjects with an available assessment. QOL measures will be summarized numerically including change from baseline and percent change from baseline to 12 months post procedure follow-up.

All safety data will be summarized descriptively and reported for the 30 days post-procedure and from 30 days to 12 months post-procedure time periods for the treatment groups.

9.2 Sample Size Justification

The sample size is determined taking into consideration the primary endpoint of complete elimination of AF burden. It is assumed that the success rate for the Control arm is 40%, and the study is designed to document superiority of EPi-Sense-AF with a 65% success rate. The sample size result, based on 2-sided α = .05, 80% power, a 2:1 allocation of EPi-Sense-AF:Control, and a 10% drop out rate, is 102:51 or 153 subjects.

9.3 Analysis Populations

The following populations will be defined for various analyses.

9.3.1 Intention To Treat (ITT) Population

The ITT population will include all study subjects who receive a randomized procedure. This population will be used for all efficacy analyses. Subjects randomized but with no post-treatment assessments will be imputed (refer to Section 9.4).

9.3.2 Modified Intention To treat (mITT) Population

The mITT population will include all study subjects who receive a randomized procedure and have at least one post-treatment follow-up visit. This population will be used for all efficacy analyses.

9.3.3 Per Protocol (PP) Population

The PP population will include all study subjects who receive their randomized procedure who have at least four of the five first year visits and who have no major protocol violations or deviations. This population will be used for the primary efficacy analysis.

9.3.4 Safety Population

The safety population will include all subjects who received a randomized procedure. They will be evaluated on the procedure received, in the event it differs from the randomized procedure. This population will be used for all safety analyses.

9.4 Primary Efficacy Endpoint Analysis

The binary primary endpoint of success or failure to achieve freedom from AF/AT/AFL absent class I and III AADs except for a previously failed or intolerant class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post procedure follow-up visit will be compared between the two treatment groups using a chi-square test using a two-sided alpha of 0.05 to determine if superiority of the treatment arm is attained.

Define P as the true percentage of subjects failing to achieve freedom. The hypothesis to test is:

$$H_o: P_T = P_C \quad \text{vs} \quad H_a: P_T \neq P_C$$

where P_T is the true failure rate for the Treatment arm and P_C for the Control arm. The formula for the chi-square test is:

$$\chi^2 = \sum_{i=1}^{m} \frac{(O_i - E_i)^2}{E_i}$$

where O_i represents the number of observed events in the ith cell and E_i represents the expected number of events in the ith cell. H_o is rejected in favor of H_a if the resulting p-value <0.05 and the estimated P_t exceeds P_c.

Subjects who were randomized but have no post-treatment assessments will be conservatively imputed as therapeutic failures at six months.

A tipping point analysis[x] will be conducted to explore the sensitivity of the results to the effect of missing data. Baseline demographics of subjects with missing data will be compared between the two treatment arms, as well as to those subjects without missing data, to explore whether there are any factors associated with having missing data.

9.5 Secondary Efficacy Endpoints Analysis

Secondary endpoints will be compared between treatment arms using either a chi-square test for binary endpoints or two-sample Z-test, for numerical endpoints. All secondary analyses will be performed on the ITT population. Change and percent change in QOL will be compared between the two treatment groups using a two-sample Z-test at each visit based on available data.

In addition, the primary analysis will be performed using the per protocol population.

9.6 Exploratory Efficacy Endpoints Analysis

The analysis for exploratory endpoints will be determined once final decisions on exploratory endpoints are made. More information on exploratory endpoints analysis will be provided in the study Statistical Analysis Plan (SAP).

9.7 Primary Safety Analysis

The primary safety analysis will be to document an acceptable risk profile. This criterion will be defined as an acceptable level of MAEs. It is estimated that the true incidence rate for MAEs in this study population is no more than 12%. A 95% one-sided confidence interval for the investigational treatment arm based on a 102 subject sample size is 5%, resulting in an upper bound of MAEs being less than 20%. This result would document an acceptable risk profile for the investigational arm.

9.8 Subgroup Analysis

A subgroup analysis will be conducted for the subgroups of gender, age, BMI, and left atrial size and volume. For each of these subgroup variables, a logistic regression model will be fit to the primary endpoint modeling for (1) treatment arm, (2) subgroup variable, and (3) interaction term of treatment arm x subgroup variable. A two-tailed alpha level of 0.15 will be used for determining poolability of results.

10.0 PATIENT INFORMED CONSENT

The sponsor, AtriCure will provide a template informed consent to study sites for review and approval by the local Institutional Review Board (IRB). The template consent may be modified to the sites institutional requirements but must include all the required regulatory consent elements. The modified consent must be submitted to the sponsor AtriCure for review prior to submitting to their Institutional IRB. All subjects must sign the IRB approved informed consent prior to enrollment in the study and the initiation of any study-related procedures.

Additionally, each subject must consent to pertinent baseline and follow-up data affected by HIPAA for transfer from the appropriate cardiologists or primary care physician office to the study site. Due to the differences in state regulations affecting HIPAA, sites may supply their local consent document or language for inclusion in the study informed consent document. A copy of the IRB approved consent must be provided to the sponsor AtriCure Surgical for their records.

11.0 RISK / BENEFIT ASSESSMENT

[x] Yan X, Lee S, Li N. Missing data handling methods in medical device trials. JNL Biopharm Stat 2009,19(6):1085-1098.

11.1 Risks Associated with the Clinical Investigation

A number of complications and adverse events that are known to occur in patients undergoing surgical or endocardial ablations for symptomatic persistent AF may be anticipated during the course of this study.

In general, the device-related complications and adverse events reported in the historical literature are:

- Cardiac arrest / myocardial infarction
- Thrombus formation (or thrombo-embolic event)
- Pulmonary vein stenosis
- Cardiac tamponade
- Pericardial effusion
- Esophageal injury
- Left atrium rupture/perforation
- Infection
- Vessel Injury
- New arrhythmias
- Neurologic complication
- Phrenic nerve palsy
- Excessive bleeding
- Death
- Complete heart block requiring permanent pacemaker
- Any other damage (e.g., burn, puncture) to other adjacent structures
- Vascular access complications
- Serious skin burn
- Pulmonary edema
- Pericarditis
- Mediastinitis.

11.2 Risk Mitigation

The protocol has been designed to minimize the risks to study subjects participating in the study. In particular:

- Safety features: Safety features incorporated into the EPi-Sense-AF Guided Coagulation System with VisiTrax minimize risks to the participating subjects.
- Investigator Selection: Only practicing cardio-thoracic surgeons who are trained and experienced in cardiac surgical procedures and in endoscopic, minimally invasive techniques will be recruited to participate as investigators and perform the epicardial ablation procedure. Only practicing electrophysiologists who are trained and experienced in AF catheter ablation procedures will be recruited to participate as investigators.
- Investigator Training: All study site investigators (Cardiac Surgeons) performing the epicardial ablation using the EPi-Sense-AF Guided Coagulation System will participate in didactic training and a device/procedure training program. The combined training programs provide each surgeon with a thorough working knowledge of the protocol, applicable regulations and proper/safe use of the EPi-Sense-AF Guided Coagulation System with VisiTrax.
  All study site investigators (Electrophysiologists) performing the endocardial catheter ablation will be experienced and will have been trained on the use of the endocardial catheter systems to be used for this study. The Electrophysiologists will be trained on the protocol and the study lesion patterns to be performed.
- Patient Selection: Potential study candidates will be carefully screened for conditions that will not put them at higher risk for adverse events during study participation.

- Subject Follow Up: Subjects participating in this clinical study will be followed at 1 month, 3 months 6 months, and 12 months post procedure to evaluate if subject is not having any adverse complications and any concerns the subject may have are being addressed. Subjects will be also be followed long-term at a 18 month post procedure office visit and an annual phone follow-up at year 2, 3, 4, and 5 post procedure.

11.3 Justification for Investigation

The EPi-Sense-AF Guided Coagulation system is used to coagulate cardiac tissue by accessing the posterior cardiac epicardium via a cannula inserted through a transdiaphragmatic or sub-xyphoid access for introducing an endoscope and surgical instruments. The endoscopic transdiaphragmatic or sub-xyphoid epicardial ablation approach makes it feasible to complete a comprehensive lesion pattern including ablation of the posterior left atrium. In addition, performing epicardial ablation along the pericardial reflections adjacent the pulmonary veins followed by endocardial catheter ablation to complete the pulmonary vein isolation and the cavotricuspid isthmus ablation to prevent typical AFL enables achieving conduction block as a truly minimally invasive approach without the need for chest incisions or ports, lung deflation, or complex dissections of the pericardial reflections.

This multicenter randomized pivotal study is necessary to evaluate the safety and efficacy of the study lesion pattern created using endoscopic epicardial ablation with endocardial catheter ablation to complete PVI. The potential benefits of a truly minimally invasive surgery for the treatment of symptomatic persistent atrial fibrillation justifies this randomized pivotal study to collect clinical data to determine the safety and efficacy of the study lesion pattern using the EPi-Sense-AF Guided Coagulation System with VisiTrax for the treatment of symptomatic persistent AF versus a standalone endocardial catheter ablation.

12.0 STUDY COMPLIANCE

12.1 Monitoring Procedures

The sponsor AtriCure or their designated CRO will be responsible for the monitoring of this study. The Clinical Research Associates (CRA) are qualified by training and experience to oversee the conduct of the study. The CRA's responsibilities include maintaining regular contact with each investigational site, through telephone contact and on-site visits, to ensure that: 1) the Investigational Plan is followed; 2) that complete, timely, and accurate data are submitted; 3) that problems with inconsistent and incomplete data are addressed; 4) that complications and Unanticipated Adverse Device Effects are reported to the Sponsor; and 5) that the site facilities continue to be adequate.

Any questions regarding these matters should be addressed to:

Shana Zink
VP Clinical Affairs
AtriCure
Tel: 513-755-4562
Fax: 513-265-0621
Email: szink@atricure.com

12.2 Study Oversight

A Data safety Monitoring Board (DSMB) and a Clinical Events Committee (CEC) will be identified for this randomized pivotal study. The DSMB and CEC will be made up of cardiothoracic surgeons, electrophysiologists (EP) or cardiologists. The DSMB will also include a biostatistician.

12.3 Monitoring Procedures

AtriCure or their designee CRO will conduct regular clinical monitoring visits to each investigational site. Before beginning data collection for a given site, a site pre-study site qualification visit will be conducted. The objectives of this pre-study visit are:

- to confirm that the Investigator and study personnel fully understand the Clinical Investigation Plan, the data collection procedures and the requirements to be met before starting the study;
- to confirm that the Investigator and study personnel fully understand the procedures related to the selection of study subjects for this study; and
- to confirm that the Investigator and study personnel have appropriate knowledge, experience and equipment to comply with the study requirements.

Observations made during a pre-study visit will be documented by means of a pre-study monitoring report.

To ensure that the Investigators and their staff members understand and accept their defined responsibilities, the Clinical Monitor will maintain regular correspondence and perform periodic site visits during the course of the study to verify the continued acceptability of the facilities, compliance with the Investigational Plan, conditions of the IRB and requirements of the IDE regulations, complete documentation and reporting of any complications and Unanticipated Adverse Device Effects, and the maintenance of complete records. Clinical monitoring will include review and resolution of missing or inconsistent results and source document checks (i.e., comparison of submitted study results to original reports) to assure the accuracy of the reported data. The Clinical Monitor will evaluate and summarize the results of each site visit in written reports, identifying any repeated data problems with the Investigator and specifying recommendations for resolution of noted deficiencies.

12.4 Data Quality Assurance

Access for data entry into the electronic data capture system developed for the study will be provided to all Investigational Sites. The Investigator/Clinical Coordinator will be responsible for completion and timely input of the study data to facilitate data processing by the Sponsor or designee.

Data entered into the data capture system will be reviewed to identify inconsistent or missing data and Adverse Events. Data problems will be addressed in calls to the Investigational Sites and during site visits. All electronic data files will be secured to ensure confidentiality.

The Investigator is to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and Informed Consents. The source documents will be used at the regular monitoring visits to verify information entered into the data capture system.

12.5 Visit Boundaries and Missed Visits

Section 6.0 defines the tolerance range for each follow-up visit. A visit that occurs outside of the specified range will be coded using the closest follow-up window and identified as a protocol deviation on the study non-compliance log located within the site regulatory binder.

12.6 Subjects Lost-to-Follow-Up

A subject will be considered lost-to-follow-up from the last missed clinical evaluation if all reasonable efforts made to contact the subject and request his continued participation in the study have failed. Telephone and written attempts will be made to locate and return such individuals to care. At least two certified letters must be sent. In instances where the individual cannot be located or traced, the circumstances leading to lost-to-follow-up status will be documented. All attempts to contact the subject will be documented.

Study ID numbers assigned to subjects who are discontinued will not be reassigned to newly enrolled subjects. Whenever possible, subjects who have been discontinued for reasons other than lost-to-follow-up will be contacted and requested to participate in ongoing safety data assessments conducted by phone.

12.7 Screened Subjects Who are Not Enrolled

Only data for enrolled/randomized subjects will be monitored and entered into the database. Subjects who are screened for the study but are not enrolled for any reason will not be followed and AtriCure will not evaluate their data. The sites may retain the screening data forms for these subjects, at their discretion.

13.0 INVESTIGATOR RESPONSIBILITIES AND OBLIGATIONS

13.1 Investigator Responsibilities

The investigator is responsible for obtaining the initial and continuing review and approval from the authorized IRB for the institution (site) at which the proposed clinical investigation is to be conducted. The Investigator is responsible for ensuring that the investigation is conducted according to the Investigator Agreement, this Investigational Plan and applicable FDA regulations as required. Investigator responsibilities are defined in Title 21 of the US Code of Federal Regulations Part 812, Subpart E.

The Investigator is responsible for ensuring that informed consent is obtained from each study subject prior to the initiation of any study procedures.

The Investigator shall permit the device to be used only under his / her supervision. Upon completion or termination of this study, or at Sponsor's request, the Investigator shall return to the Sponsor any remaining unused devices or otherwise dispose of the device as the Sponsor directs.

13.2 Investigator Records

The Investigator will maintain complete, accurate and current study records, including the following materials:

1 Correspondence with the Sponsor, the Clinical Monitor, the Medical Monitor, other Investigators, the IRB, or the FDA;
2 Accountability of records of receipt, use, and disposition of all investigational devices and other study materials, including:
   - type and quantity of the device
   - dates of its receipt
   - lot number
   - names of all persons who were treated with the device
   - number of devices disposed of
   - the number of devices that have been returned to the Sponsor, or otherwise disposed of, and the reason for such action;
3 Study Subject Records, including Informed Consent forms, supporting documents (ECG printouts, ECG & ECHO data printout and medical records, etc.), and records of exposure of each study subject to the device;
4 Documentation of any use of the device without Informed Consent. A brief description of the circumstances justifying the failure to obtain Informed Consent and written concurrence of a licensed physician are required;
5 All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated);
6 Current study protocol and protocol deviation log, with dates and details of any reason for deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects;

7 The approved blank Informed Consent form and blank eCRFs;
8 Documentation that the Investigational Plan has been approved by all of the necessary approving authorities; and
9 Signed Investigator's Agreements with CV's of the Principle Investigator and all participating Co-Investigators.

These records shall be maintained for a period of 2 years after the later of the following two dates:

- date on which the investigation is terminated or completed; or
- date that the records are no longer required for purposes of supporting a premarket approval application or notice of completion of a product development protocol.

13.3 Investigator Reports

The Investigator will be responsible for the following reports:

Unanticipated Adverse Device Effect: An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, or any life threatening problem or death caused by, or associated with the device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this investigational plan; or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of the subjects.

The Investigator shall report all Unanticipated Adverse Device Effects to the Sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

All Unanticipated Adverse Device Effects should be documented in the electronic data capture system documenting time of onset, a complete description of the event, severity, duration, actions taken and event outcome.

Withdrawal of IRB Approval: The Investigator shall report to the Sponsor within 5 working days if, for any reason, the IRB withdraws approval to conduct the investigation. The report will include a complete description of the reason(s) for which approval was withdrawn.

Deviations from the Investigational Plan: The Investigator shall notify the Sponsor and the reviewing IRB of any changes in, or deviations from, the Investigational Plan to protect the life or physical well being of the Subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurs. Except in such emergency, prior approval by the Sponsor is required for changes in or deviations from the plan; and, if these changes or deviations may affect the scientific soundness of the plan, or the rights, safety or welfare of the subjects, FDA and / or IRB approval also is required.

Use of device labeled For Investigational Use Only without Informed Consent: No Subject may be treated with the device labeled For Investigational Use Only without prior Informed Consent. Such treatment constitutes a violation of federal regulations. If the Investigator treats a Subject with the device labeled For Investigational Use Only without prior Informed Consent that Investigator must report this use to the Sponsor and the reviewing IRB within 5 working days after use occurs.

Progress Reports: The Investigator is required to submit annual progress reports to the study Sponsor and to the reviewing IRB. Reports must include the number of study subjects, a summary of all follow up evaluations, a summary of all adverse events and a general description of the study's progress.

Final Report: The Investigator will submit a final report to the Sponsor and to the IRB within 3 months of termination of the study or termination of that Investigator's participation in the study.

Other Reports: Upon request of the Sponsor, the FDA or the IRB, the Investigator shall provide accurate, complete and current information.

13.4 Investigator Agreement

An example of the agreements to be entered into by all investigators to comply with investigator obligations is provided for review.

We understand that, prior to the initiation of the study, we must provide FDA with a certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement. This certification will be provided once the investigators have been identified and have signed the investigator agreement.

13.5 Financial Disclosure by Clinical Investigators

We understand that, pursuant to 21 CFR part 54 and prior to the initiation of the study, each investigator must disclose certain financial arrangements that may exist between that investigator and AtriCure This information will be collected from each investigator, maintained in confidential files at AtriCure and will be available for review by FDA upon request. The Sample Financial Disclosure is provided for review.

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Attachment A

Treatment Arm Study Procedure

Convergent Epicardial and Endocardial Ablation Procedure

Preoperative requirements and patient preparation should follow the Investigator's and site's standard of practice for closed chest, endoscopic epicardial and endocardial ablation procedures.

Follow the standard lesion creation steps described below. Access the anatomical locations endoscopically, and create the epicardial lesion pattern which includes ablating the posterior left atrium between the left and right pulmonary veins. If additional lesion(s) are created or suggested lesions are not created, this must be entered into the electronic data capture system developed for the study.

The completion of each lesion may require multiple sequential placements. The lesions to be created in the treatment arm are as follows:

Trans-Diaphragmatic Endoscopic Access

Using standard laparoscopic surgical techniques for creating a pericardial window, obtain trans-diaphragmatic access to the posterior surface of the heart. Create an incision 3cm below the xyphoid in the midline of the abdomen. Using abdominal CO_2 insufflation, create an incision through the central tendon of the diaphragm, above the liver and medial to the falciform ligament. The cannula provides direct access to the posterior surface of the heart and is sized to create space between the epicardium and the pericardium to visualize cardiac structures and manipulate the coagulation device alongside an endoscope, so all device manipulations are performed under direct visualization.

After obtaining trans-diaphragmatic access, the Epi-Sense®-AF Guided Coagulation Device with VisiTrax®, cannula, scopes and surgical instruments are used to create the epicardial lesion pattern.

Sub-Xyphoid Endoscopic Access

Using standard surgical techniques for creating a pericardial window superior to the diaphragm, obtain access to the posterior surface of the heart. Create an incision immediately inferior to the xyphoid process. Direct visualization of the pericardium superior to the diaphragm can be achieved through the incision. The xyphoid process may be removed, dependent on patient anatomy. A 2 cm incision should be made in the pericardium to allow access for the cannula. The cannula provides direct access to the posterior surface of the heart and is sized to create space between the epicardium and the pericardium to visualize cardiac structures and manipulate the coagulation device alongside an endoscope, so all device manipulations are performed under direct visualization.

After obtaining Sub-Xyphoid access, the Epi-Sense®-AF Guided Coagulation Device with VisiTrax®, cannula, scopes and surgical instruments are used to create the epicardial lesion pattern.

Esophageal Temperature Monitoring

Esophageal temperature monitoring should be utilized during epicardial and endocardial ablation. At least one esophageal temperature probe should be positioned near the left atrium under fluoroscopic guidance. All other instrumentation including NG and OG tubes, and TEE probes need to be removed prior to placement of the esophageal temperature probe. Whenever possible, the position of the probe should be interrogated with fluoroscopy to ensure proximity to the ablation electrode (epicardial or endocardial). If esophageal temperature increases more than 0.5°C during lesion creation or above an absolute maximum of 38.0°C, RF energy should be terminated until the temperature reduces to baseline.

Ablating Epicardial Tissue – The EPi-Sense-AF Device

Epicardial lesions are created using the EPi-Sense-AF coagulation (e.g. "ablation") device. The device integrates vacuum contact that ensures continuous lesions with saline perfusion to cool the device surface not contacting epicardium and enable creating full thickness lesions. The addition of sensing electrodes helps guide energy delivery augmenting ablation directionality and detection of lesion completeness.

- Vacuum is coupled to the ablation electrode ensuring the electrode contacts the epicardium. Consistent contact pressure ensures controllable heating along the electrode especially since the electrode incorporates a helical coil where individual windings are separated to allow vacuum to pull tissue into engagement with each winding such that the current density profile produces a continuous lesion along tissue pulled into engagement with the electrode. A stopcock allows turning vacuum on and off. When moving the ablation electrode to another location, the stopcock should be actuated to discontinue vacuum until positioned at the target location.
- A separate perfusion lumen is connected to an unpressurized bag of saline. The perfusion lumen is coupled to the vacuum lumen such that when a vacuum seal is created, saline is pulled through the device at a set rate to cool the device so the heating is only directed into epicardium. Additionally, controlling the power, contact pressure, and perfusion allows controlled energy delivery to create consistent lesions that are continuous and extend to the endocardium with a reliable depth up to 7 mm.[xi]
- The sensing electrodes on the EPi-Sense-AF device may be utilized to monitor cardiac electrograms, transmitted through the sensing electrodes and to an external EP Recorder, in order to confirm appropriate positioning of the EPi-Sense-AF coagulation electrodes against atrial tissue. The sensing electrodes may be interrogated before coagulation is initiated but after vacuum creates a seal and ensures the sensing electrodes and coagulation electrode engage tissue. When an atrial signal is identified, augmented by direct endoscopic visualization of device placement, energy may be transmitted through the coagulation electrode to create the desired lesion. When no signal or a ventricular signal is identified, then placement of the coagulation electrode relative to the left atrium should be re-evaluated.
- Once position is confirmed visually and by interrogating the electrograms, RF energy is delivered to create each lesion.
- During lesion creation, the electrograms should be interrogated for amplitude reduction that delineates the creation of a full thickness lesion capable of interrupting electrical propagation. This may be especially useful when epicardial fat causes several power-downs during RF energy delivery. The generator incorporates a safety mechanism to avoid overheating tissue by monitoring impedance and reducing power if impedance increases at a rate above a set threshold; afterward, the generator ramps power to its set value unless another power-down condition (e.g. impedance rise) is detected. This function reduces the incidence of vaporization but may be a bit conservative when ablating over fat since the differences in electrical impedance between fat and muscle produces more rapid heating of fat that causes more frequent power-downs and lower efficiency of heating. As such, when ablating over fat, it is beneficial to ablate more than once to obtain the same full thickness lesion; a requirement that evaluating the change in electrograms will help guide.
- Saline may be inserted through the cannula to cool the pericardial space during epicardial ablation. When partially filling the pericardial space with fluid, a stopcock connected to the cannula vacuum lumen is turned off until after ablation, when the fluid is removed. Whenever, esophageal temperature increases, saline may be used to flush and cool the pericardial space reducing esophageal temperature.
- After creating each lesion, the position and extent are interrogated by visually

[xi] Garrett HE, et al. Evaluation of an unipolar RF coagulation system for epicardial AF ablation in chronic GLP canine models. J Innov Card Rhythm Man. 2012;3:1042-1048.

inspecting the demarcation that delineates ablated epicardium.

Epicardial Lesion Locations

Left Posterior Pulmonary Vein Orifice Lesion

- The posterior left pulmonary vein lesion(s) should be created adjacent the pericardial reflections along the left pulmonary veins. The location of this lesion(s) should be entirely on the left atrium near the orifice and not extend onto the pulmonary veins themselves.
- Under direct endoscopic visualization with an endoscope in the cannula, the coagulation device is advanced through the cannula and above the guidewire so it contacts the left atrium adjacent the left pulmonary veins. The device remains straight as it is positioned against the left atrium adjacent to the left pulmonary veins. The guidewire may function as an arm to help urge the coagulation device into position along the left atrium.

Right Posterior Pulmonary Vein Orifice Lesion

- The posterior right pulmonary vein lesions should be created adjacent the pericardial reflections along the right pulmonary veins. The location of these lesions should be entirely on the left atrium near the orifice and not extend onto the pulmonary veins themselves. These lesions should extend from the superior pericardial reflection adjacent the right superior pulmonary vein to the junction between the right inferior pulmonary vein and the inferior vena cava.
- Under direct endoscopic visualization with an endoscope in the cannula, the coagulation device is advanced through the cannula and above the guidewire so it contacts the left atrium adjacent the right pulmonary veins. The device remains straight as it is positioned against the left atrium adjacent to the right pulmonary veins.

Posterior Parallel Vertical Connecting Lesions

- Identify electrical activity for degree of baseline electrical activity.
- Connecting lesions oriented parallel to each other and extending superior to inferior are created along the posterior left atrium between the left and right pulmonary veins. Number of parallel vertical lesions will depend on the size of the left atrium and the pericardial reflections' anatomy. The posterior left atrium bounded by the pericardial reflections between the two sets of pulmonary veins (left and right) should be ablated so that subsequent pacing of the posterior left atrium in this region is unable to capture thereby demonstrating exit block and posterior isolation. Alternatively, mapping of this region should delineate scar tissue indicative of ablated tissue.

Left Anterior Pulmonary Vein Orifice Lesion

- Position the cannula around the left pulmonary veins to access the left anterior pulmonary vein orifice posterior to the left atrial appendage. Identify the left pulmonary veins to position the coagulation device along the pulmonary vein orifice.
- Under direct endoscopic visualization, position the device through the cannula, and along the anterior orifice of the left pulmonary veins towards the transverse sinus and the ligament of marshall such that the coagulation device remains posterior to the left atrial appendage.
- Ensure the exposed electrode of the device contacts the left pulmonary vein orifice. Utilize the sensing electrodes to augment confirmation of device position prior to initiating RF energy delivery.
- Create a lesion that extends from the posterior left pulmonary vein lesion, along the anterior left pulmonary vein orifice, and past the ligament of marshall (LOM) to ablate the LOM.

Right Anterior Pulmonary Vein Orifice Lesion

- Move the cannula around the inferior vena cava to access the interatrial groove under the right atrial appendage. Identify the superior vena cava and the right pulmonary veins to position the coagulation device along the right pulmonary vein orifice.
- Under direct endoscopic visualization position the device through the cannula, and along the anterior orifice of the right pulmonary vein.
- Ensure the exposed electrode of the device contacts the right pulmonary vein orifice adjacent the interatrial groove. Utilize the sensing electrodes to augment confirmation of device position prior to initiating RF energy delivery.
- Create a lesion that extends from the transverse sinus under the superior vena cava, along the left atrium at the orifice to the right pulmonary vein antrum, to the oblique sinus between the right pulmonary vein antrum and the inferior vena cava.

Transitioning Between Epicardial and Endocardial Components

Closing Epicardial Access Sites

- After completing all epicardial lesions and interrogating the pericardial space to ensure hemostasis, a pericardial drain is inserted through the cannula and into the pericardial space ensuring the drain is sized such that the vacuum segment resides within the pericardial space. The cannula is removed leaving the drain in place and the free end is pulled through one of the abdominal punctures utilizing a clamp or other surgical instrument. If a sub-xyphoid access has been utilized, a puncture incision shall be created lateral to the central incision to pass the free end of the drain out of the patient. The free end of the drain is connected to a vacuum bulb to monitor drainage throughout the endocardial component of the procedure.
- Prior to closing abdominal incisions, hemostasis throughout the abdominal cavity should be interrogated. Abdominal incisions will be closed in standard fashion utilizing standard general surgical techniques to reduce the potential for incisional hernias.

Endocardial Vascular Access

- After closing all epicardial access sites, navigation patch positions are confirmed and patient draping for catheter ablation is adjusted. Using standard catheterization and sheath introduction techniques, access to the venous vasculature is obtained.
- A coronary sinus catheter is introduced to help monitor atrial electrograms, serve as a reference catheter for 3-D navigation, and provide electrodes from which pacing stimuli can be transmitted.
- Transeptal access is then obtained by puncturing the fossa ovalis under ultrasound (ICE or TEE) guidance to provide access to the left atrium. Two transeptal sheaths may be utilized to facilitate insertion of an ablation catheter and diagnostic circular catheter into the left atrium. In certain circumstances, the ablation catheter may be inserted through the transeptal puncture site without the need for a sheath.
- Before or after transeptal access is obtained, heparin needs to be administered to assure ACTs between 300 and 400 seconds to protect against thrombus formation while catheter instrumentation resides within the left atrium.
- Mapping of the epicardial lesions in terms of locations and extents helps identify the breakthrough locations at the pericardial reflections and guides endocardial ablation. Voltage maps are not required to identify breakthrough locations but may be used to augment identification of breakthrough locations if desired.

Ablating Endocardial Tissue

- Specific endocardial lesions will be created with an open irrigated-tip RF ablation catheter having unidirectional or bidirectional steering.
- Specific commercially available RF ablation systems that may be utilized during the study may include Therapy™ Cool Path™ family of Irrigated Ablation Catheter and

associated accessories (St. Jude Medical, Inc.), Saffire BLU™ family of Ablation Catheter and associated accessories (St. Jude Medical, Inc.), or ThermoCool® family of Irrigated Tip Catheter and Integrated Ablation System (Biosense, Webster).
- 3-D navigation utilizing a Carto™ EP Navigation System (Carto 3 or Carto XP), or an EnSite™ System (NAVx™ or Velocity™) may be utilized to monitor the position of the ablation catheter electrode, facilitate endocardial mapping, and record ablation locations.

Endocardial Connecting Lesions

Right Superior Pulmonary Vein Lesions

- Using standard pulmonary vein isolation techniques, the epicardial lesions should be connected at breakthrough locations along the pericardial reflections adjacent the right superior pulmonary veins to complete isolation of the right pulmonary veins and produce a barrier against signal propagation from the PVs to the left atrium and vice versa. A circular catheter may be utilized to identify the gaps along the pericardial reflection that needs to be ablated endocardially. Point lesions are created with a saline irrigated ablation catheter and standard left-sided catheter ablation techniques such that they interconnect into a series that connect the epicardial linear lesions together.
- Since two pericardial reflections (one superior and one inferior) connect the pericardium to the left atrium adjacent the right pulmonary veins, both gap locations should be ablated prior to evaluating pulmonary vein isolation. Even if the superior gap is ablated, the carina allows communication from the inferior pulmonary vein to the superior vein and vice versa. Only ablating both gaps along the pericardial reflections will produce isolation of the right pulmonary veins.
- Pulmonary vein isolation should be confirmed using entrance and/or exit block to ensure the breakthrough locations at the pericardial reflections have been adequately closed.

Right Inferior Pulmonary Vein Lesions

- Using standard pulmonary vein isolation techniques, the epicardial lesions should be connected at breakthrough locations along the pericardial reflections adjacent the right inferior pulmonary veins to complete isolation of the right pulmonary veins and produce a barrier against signal propagation from the PVs to the left atrium and vice versa. A circular catheter may be utilized to identify the gaps along the pericardial reflection that needs to be ablated endocardially. Point lesions are created with a saline irrigated ablation catheter and standard left-sided catheter ablation techniques such that they interconnect into a series that connect the epicardial linear lesions together.
- Since two pericardial reflections (one superior and one inferior) connect the pericardium to the left atrium adjacent the right pulmonary veins, both gap locations should be ablated prior to evaluating pulmonary vein isolation. Even if the superior gap is ablated, the carina allows communication from the inferior pulmonary vein to the superior vein and vice versa. Only ablating both will produce isolation of the right pulmonary veins.
- Pulmonary vein isolation should be confirmed using entrance and/or exit block to ensure the breakthrough locations at the pericardial reflections have been adequately closed.

Left Superior Pulmonary Vein Ridge Lesions

- Using standard pulmonary vein isolation techniques, the epicardial lesions should be connected at breakthrough locations along the pericardial reflections adjacent the left

superior pulmonary veins and along the ridge between the pulmonary veins and the left atrial appendage to complete isolation of the left pulmonary veins and produce a barrier against signal propagation from the PVs to the left atrium and vice versa. A circular catheter may be utilized to identify the gap along the pericardial reflection that needs to be ablated endocardially. Point lesions are created with a saline irrigated ablation catheter and standard left-sided catheter ablation techniques such that they interconnect into a series that connect the epicardial linear lesions together.

- Pulmonary vein isolation should be confirmed using entrance and/or exit block to ensure the breakthrough locations at the pericardial reflections have been adequately closed.

Induced or Organized Atrial Arrhythmias

- If atrial fibrillation organizes into an atrial arrhythmia (AFL, AT, AVNRT, etc.) or if an atrial arrhythmia is induced during Isoproterenol administration or rhythm challenging exercises, then mapping and localized endocardial ablation may be performed to target the specific atrial arrhythmia.
- CFAE ablation and linear endocardial lesions outside the prespecified pattern should be avoided.

Cavotricuspid Isthmus (Typical Atrial Flutter) Lesions

- After creating all left atrial lesions, sheaths may be removed from the left atrium and heparinization interrupted characteristic of no longer needing to maintain ACTs 300 to 400 seconds without instrumentation in the left atrium.
- Irrespective of inducibility, a cavotricuspid isthmus, right atrial typical flutter lesion should be created.
- Using standard endocardial ablation techniques, a segment of right atrium defining the cavotricuspid isthmus between the inferior vena cava and the tricuspid valve is ablated to interrupt a known pathway for typical atrial flutter.
- Bidirectional block should be confirmed across the isthmus lesion to ensure integrity of the connecting point ablations.

Post-Operative Management

- Drainage from the pericardial drain should be interrogated to monitor potential for bleeding or fluid build-up that could cause a pericardial effusion prior to removal. Recommendation from best practice symposiums is to leave the drain in place until drain output is less than a threshold of 50-100cc in a 24 hr period.
- A trans-thoracic echocardiography will be performed at 7+7 days post-operative to evaluate the patient for pericardial effusion.
- Recommendation from best practice symposiums is to administer a prophylactic regimen of steroids (and/or non-steroidals) to prevent Dressler's Syndrome, Pericarditis, and other inflammatory mechanisms that have been shown to cause late pericardial effusions, provided the patient is able to tolerate such regimen.
    - Example #1: 2 mg/ kg hydrocortisone immediately post-op; and 1 mg/kg of prednisone on Post-op day 1 and Post-op day 2.

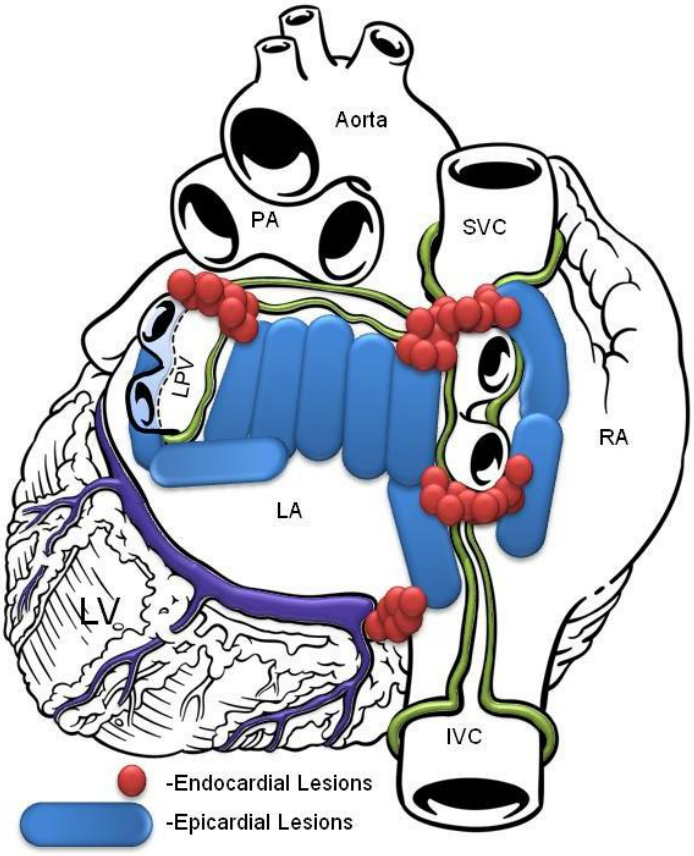
Convergent Epicardial and Endocardial Lesion Pattern

Epicardial Lesions [blue]

1 Right Posterior Pulmonary Vein Lesions
2 Left Posterior Pulmonary Vein Lesions
3 Parallel Posterior Vertical Connecting Lesions
4 Right Anterior Pulmonary Vein Lesions
5 Left Anterior Pulmonary Vein Lesions

Endocardial Lesions [red] (Located at Pericardial Reflections)

6 Right Superior Pulmonary Vein Lesions
7 Right Inferior Pulmonary Vein Lesions
8 Left Superior Pulmonary Vein Ridge Lesions
9 Cavotricuspid Isthmus (Typical Atrial Flutter) Lesions



Attachment B

Control Arm Study Procedure

Endocardial Catheter Ablation Procedure

Endocardial Catheter Ablation Procedure

Preoperative requirements and patient preparation should follow the Investigator's and site's standard of practice for left-sided catheter ablation procedures.

Follow the suggested lesion creation steps described below. Access the anatomical locations endocardially, and create the lesion pattern which includes isolating the left and right pulmonary veins, connecting the PV isolation lesions with an atrial roof lesion, performing < 30 minutes of CFAE ablation if the rhythm does not convert into SR or organize into an AFL/AT, mapping and ablating AFLs/ATs induced, and ensuring bidirectional block across a cavotricuspid isthmus lesion. If additional lesion(s) are created or suggested lesions are not created, this must be entered into the electronic data capture system developed for the study.

Endocardial Access

- Using standard catheterization and sheath introduction techniques, access to the venous vasculature is obtained.
- A coronary sinus catheter is introduced to help monitor atrial electrograms, serve as a reference catheter for 3-D navigation, and provide electrodes from which pacing stimuli can be transmitted.
- For transeptal procedures, heparin needs to be administered to assure ACTs of 300 to 400 seconds to protect against thrombus formation while catheter instrumentation resides within the left atrium.
- Transeptal access is obtained prior to or after fully heparinizing the patient. Transeptal access is obtained by puncturing the fossa ovalis under ultrasound (ICE or TEE) guidance to provide access to the left atrium. Frequently, two trasseptal sheaths may be utilized to facilitate insertion of an ablation catheter and diagnostic circular catheter into the left atrium. Alternatively, the ablation catheter may be inserted through the transeptal puncture site without the need for a sheath.

Esophageal Temperature Monitoring

Esophageal temperature monitoring should be utilized during endocardial ablation. At least one esophageal temperature probe should be positioned along the left atrium under fluoroscopic guidance. All other instrumentation including NG and OG tubes, and TEE probes need to be removed prior to placement of the esophageal temperature probe. Whenever possible, the position of the probe should be interrogated with fluoroscopy to ensure proximity to the ablation electrode. If esophageal temperature increases more than 0.5°C during lesion creation or above an absolute maximum of 38.0°C, RF energy should be terminated until the temperature reduces to baseline.

Ablating Endocardial Tissue

- Specific endocardial lesions will be created with an open irrigated-tip RF ablation catheter having unidirectional or bidirectional steering.
- Specific commercially available RF ablation systems that may be utilized during the study may include Therapy™ Cool Path™ family of Irrigated Ablation Catheter and associated accessories (St. Jude Medical, Inc.), Saffire BLU™ family of Ablation Catheter and associated accessories (St. Jude Medical, Inc.), or ThermoCool® family of Irrigated Tip Catheter and Integrated Ablation System (Biosense, Webster).
- 3-D navigation utilizing a Carto™ EP Navigation System (Carto 3 or Carto XP), or an EnSite™ System (NAVx™ or Velocity™) may be utilized to monitor the position of the ablation catheter electrode, facilitate endocardial mapping, and record ablation locations.

Endocardial Lesions

The completion of each lesion described below may require multiple sequential placements. The suggested sequence of steps for lesion creation, are as follows:

Left Pulmonary Vein Encircling Lesions

- Using standard pulmonary vein isolation techniques, lesions encircling the left pulmonary veins should be created. A circular catheter may be utilized to guide creation of point lesions that interconnect into a series capable of interrupting propagation of electrical signals from the atrium to the pulmonary veins and vice versa.

Right Pulmonary Vein Encircling Lesions

- Using standard pulmonary vein isolation techniques, lesions encircling the right pulmonary veins should be created. A circular catheter may be utilized to guide creation of point lesions that interconnect into a series capable of interrupting propagation of electrical signals from the atrium to the pulmonary veins and vice versa.

Anterior Left Atrial Roof Connecting Lesions

- A left atrial roof lesion composing point ablations that connect the right and left pulmonary vein encircling lesions should be completed. This series of connecting point lesions should be interrogated to ensure completeness of the line capable of interrupting the propagation of electrical signals.

Additional Endocardial Left Atrial Lesions

- If the rhythm does not organize into an atrial tachycardia (AT) or atrial flutter (AFL), or convert to sinus rhythm after completing pulmonary vein isolation (PVI) and the roof lesion, then the electrophysiologist may spend up to 30 min performing CFAE ablation. The electrophysiologist may elect to convert the patient into sinus rhythm prior to endocardial mapping and ablation without performing CFAE ablation. CFAEs should be defined as constant activities or local activity with electrogram cycle length <120 msec.[xii,xiii] CFAE ablation must not involve creating linear lesions.
- If the patient still does not organize into an AT, AFL, or SR after CFAE ablation then the patient should be converted by administering Ibutilide or electrical cardioversion.

Induced or Organized Atrial Arrhythmias

- If atrial fibrillation organizes into an atrial arrhythmia (AFL, AT, AVNRT, etc.) or if an atrial arrhythmia is induced during Isoproterenol administration or rhythm challenging exercises, then mapping and localized endocardial ablation may be performed to target the specific atrial arrhythmia.

Cavotricuspid Isthmus (Typical Atrial Flutter) Lesions

- After creating all left atrial lesions, sheaths may be removed from the left atrium and heparinization interrupted characteristic of no longer needing to maintain ACTs of 300 to 400 seconds without instrumentation in the left atrium.

[xii] Knecht S, et al. Impact of pharmacological autonomic blockade on complex fractionated atrial electrograms. J Cardiovasc Electrophysiol. 2010;21(7):766-702.
[xiii] Oral H, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol. 2009;53:782-9.

- Irrespective of inducibility, a cavotricuspid isthmus, right atrial typical flutter lesion should be created.
- Using standard endocardial ablation techniques, a segment of right atrium defining the cavotricuspid isthmus between the inferior vena cava and the tricuspid valve is ablated to interrupt a known pathway for typical atrial flutter.
- Bidirectional block should be confirmed across the isthmus lesion to ensure integrity of the connecting point ablations.

Endocardial Lesion Pattern

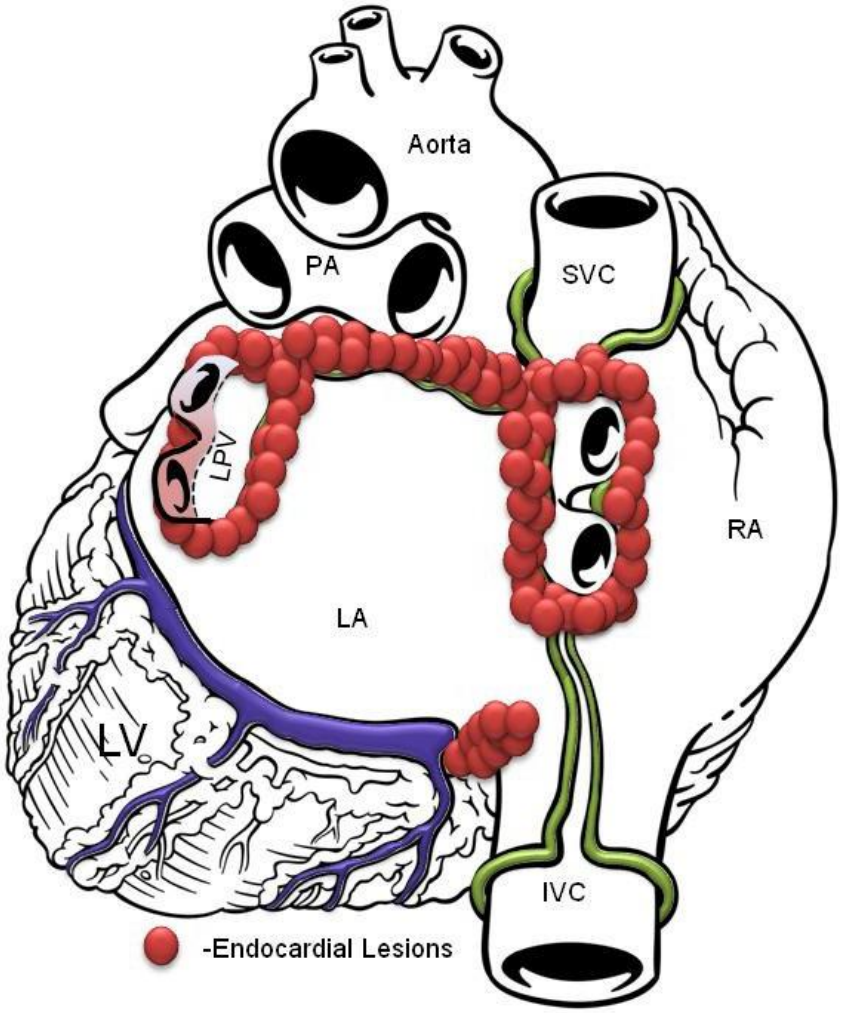
Endocardial Lesions

1 Left Pulmonary Vein Encircling Lesions

2 Right Pulmonary Vein Encircling Lesions

3 Anterior Left Atrial Pulmonary Vein Roof Connecting Lesions

4 Cavotricuspid Isthmus (Typical Atrial Flutter) Lesions



Attachment C

PV Conduction Block Confirmation Protocol

PV Conduction Block Confirmation Protocol

Testing Conduction block in the Pulmonary Veins (PVs)

Procedure to test for conduction block must be performed and conduction block should be confirmed after the protocol required lesion pattern has been created. The pacing and / or electrogram recording equipment standard for the EP Lab at the site should be used to test for conduction exit or entrance block.

To Test block:

- Use an ablation device or diagnostic circular catheter to record electrograms from, and/or transmit pacing stimuli to the pulmonary vein antrum distal to the lesion, away from the left atrium.

Exit Block Testing:

- Ensure patient is in sinus rhythm. If patient is not in sinus rhythm, attempt to cardiovert the patient into sinus rhythm in order to pace
- Connect catheter pacing electrodes to EP stimulator
- Set pacing amplitude to ≥10 mA
- Ensure pacing rate is greater than the baseline heart rate
- Confirmation is achieved by not capturing heart rate despite transmitting pacing pulses to the PV antrum (for PVI).

Entrance Block Testing

- Patient may be in AF when testing entrance block
- Connect sensing electrodes of an ablation catheter or diagnostic circular catheter to an EP recording system
- Monitor cardiac electrograms from sensing electrodes in bipolar orientation
- Place sensing electrodes on PV antrum distal to the PV isolation lesion(s) for demonstrating PVI

Confirmation of Pulmonary Vein Isolation (PVI) is achieved by determining lack of electrogram signals on PVs, inability to capture when pacing the PVs, or dissociation of cardiac signals along PVs from resting heart demonstrating PV isolation.

Attachment D

Anti-Arrhythmic Therapy Protocol

Anti-Arrhythmic Therapy Protocol

The protocols for the use of class I or III AADs recommended in the 2012 HRS/EHRA/ECAS expert consensus statement and the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with AF should be followed to manage the AAD therapy for subjects enrolled in both arms of the study.

Post procedure, subjects enrolled in both arms of the study should be prescribed class I or class III AADs the subject was taking prior to study enrollment or another failed class I or III AAD. Subjects who have a contraindication for class I or class III AADs should be followed as medically indicated.

All subjects should be weaned off their class I or III AAD at their 3 month post procedure follow-up visit unless the AADs are medically indicated or the subject is maintained on the same or lower dose of a previously failed class I or III AAD and the attending physician recommends continuation of such medical management prophylactically.

Attachment E

Anticoagulation Protocol

Anticoagulation Protocol

The anticoagulation strategies recommended in the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation for atrial fibrillation should be followed to manage the anticoagulation therapy for subjects enrolled in both arms of the study.

Pre-procedure

- Systemic anticoagulation at a therapeutic level should be maintained 3 to 4 weeks prior to the procedure.
- A TEE or ICE evaluation should be performed prior to the ablation procedure, to evaluate for the presence or absence of left atrial thrombus.
- The presence of a left atrial thrombus is an intra-op study exclusion.

During the procedure

- An ACT of 300 to 400 secs should be maintained during the endocardial catheter ablation procedure.
- Administration of protamine following ablation to reverse heparin should be considered.

Post-procedure

- Systemic anticoagulation therapy should be initiated for all patients post procedure through at least two months following the ablation procedure.
- Decisions regarding the use of systemic anticoagulation more than two months following ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF.
- Discontinuation of systemic anticoagulation therapy post ablation is generally not recommended in patients who are at high risk of stroke as estimated by currently recommended schemes ($CHADS_2$ or $CHA_2DS_2VAS_C$).

Attachment F

Repeat Catheter Ablation Protocol

Repeat Catheter Ablation Protocol

In the event that an AF/AFL/AT reoccurs post procedure for a subject in either the treatment arm or control arm of the study and a repeat catheter ablation procedure is performed, various diagnostics should be performed to evaluate reasons for failure of the index procedure.

Voltage mapping to be performed to determine and document the breakthrough locations and extents

Interrogate and Complete Pulmonary Vein Isolation

- Pulmonary vein isolation should be determined for each vein and documented as to whether they remained isolated or did they reconnect.
- The location and extent of breakthroughs to the reconnected pulmonary veins should be determined for each vein and documented.

Interrogate Reoccured Posterior Electrical Activity

- The posterior left atrium should be evaluated with respect to electrical activity. Voltage mapping should be performed to document the degree of electrical silencing along the posterior left atrium.

Document Ablation Locations

- All endocardial ablation locations should be documented; 3-D navigation tools help to identify and document the locations and extents of endocardial ablation.