Clinical Study Protocol

Low voltage-Directed Catheter Ablation for Atrial Fibrillation (LD-CAF)
LD-CAF Trial

Devices:

- **Ablation catheters with contact force capability**
- **Multi-electrode mapping catheter to be used in the left atrium**
- **3-D electroanatomical mapping system**
- **Implantable Loop Recorder**

Version: **1.2 06 Dec 2016**

Sponsor:

The MetroHealth System
MetroHealth Medical Center
2500 MetroHealth Dr.
Cleveland, Ohio 44109

Investigator (Please Print): _____

Investigator Signature: _____**Date**

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Institution: _____

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Protocol Summary

Title:	Low Voltage-Directed Ablation for Atrial Fibrillation (LD-CAF)
Design:	Prospective, multi-center, randomized, evaluation comparing the protocol specified ablation approach to the current standardized ablation approach in the treatment of non-paroxysmal atrial fibrillation.
Purpose:	To evaluate long term success of non-paroxysmal ablation when using a 1) specified low voltage-directed with pulmonary vein isolation **(LD+PVI)** approach compared, 2) empiric posterior wall isolation with pulmonary vein isolation **(PW+PVI)** approach compared to an approach of pulmonary vein isolation **(PVI)** alone.
Enrollment:	A minimum of 288 evaluable subjects. 96 subjects in each arm.
Devices:	Electro-anatomical Mapping System: • Mapping - 3D mapping platform • Diagnostic catheters – Mapping Catheter • Treatment catheters – Contact Force-Sensing Catheter
Clinical Sites:	A minimum of 4 centers will enroll over a period of 18 months.
Subject Population:	Subjects with drug refractory non-paroxysmal AF.
Endpoints:	The primary endpoint is freedom from sustained (>30 seconds) or symptomatic atrial fibrillation or atrial tachycardia without the continued use of an antiarrhythmic medication between the 3 month blanking period and 1 year post-ablation. The safety endpoint is the incident of procedure related adverse events. The secondary endpoint is atrial arrhythmia burden and need for AAD for the study ablated arrhythmia or related arrhythmia at 1 year.

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1.0 Introduction

1.1 Background

Catheter ablation for symptomatic atrial fibrillation has emerged as successful therapy for patients with medically refractive atrial fibrillation. Nearly uniform superior short- and long-term success rates compared with antiarrhythmic medications have prompted recent guideline changes that suggest ablation can be considered before use of pharmacologic therapies[1].

Patients that undergo ablation for paroxysmal atrial fibrillation benefit from high success rates. However those with persistent and long-standing persistent atrial fibrillation or moderate-severe structural heart disease continue to experience suboptimal results and often require multiple ablations[2]. As such, the ideal ablation strategy in these patients remains to be defined. Early use of a linear ablation to replicate the surgical Maze procedure improved outcomes up to 1 year, but long-term proarrhythmia from incomplete lines and residual arrhythmic substrate continue to plague the approach[1-3].

Recent work has focused more on targeted ablation approaches in patients with persistent and long-standing persistent atrial fibrillation. Additional ablation of complex fractionated electrograms (CFAE), ganglion plexi, and rotors/drivers have all improved outcomes up to 1 year after ablation. Success rates of these approaches are largely dependent on operator experience, inter-operator variability in interpretation of target sites, prolongation of procedural times, and limitations with current mapping tools[4-10].

The anatomic correlates for these additional ablation sites are largely unknown. Atrial fibrosis and low voltage are felt to serve as sources of micro and macro reentry, anchoring of rotors, and rapid drivers. As such, regional fibrosis and low voltage have been promoted as sources of atrial fibrillation arrhythmia maintenance in patients that progress to persistent and longstanding persistent atrial fibrillation[11, 12]. Therefore, incorporating low voltage and homogenizing its boarders with ablation may isolate arrhythmia promoting regions and improve long-term success rates with catheter ablation.

1.2 Pilot Study Design

This hypothesis was investigated in a recent retrospective randomized pilot trial. In this study, low voltage-directed ablation of posterior wall in addition to pulmonary vein isolation was compared to an ablation strategy of pulmonary vein

isolation with additional ablation along the posterior wall based upon operator discretion without low voltage quantification (Figure 1).

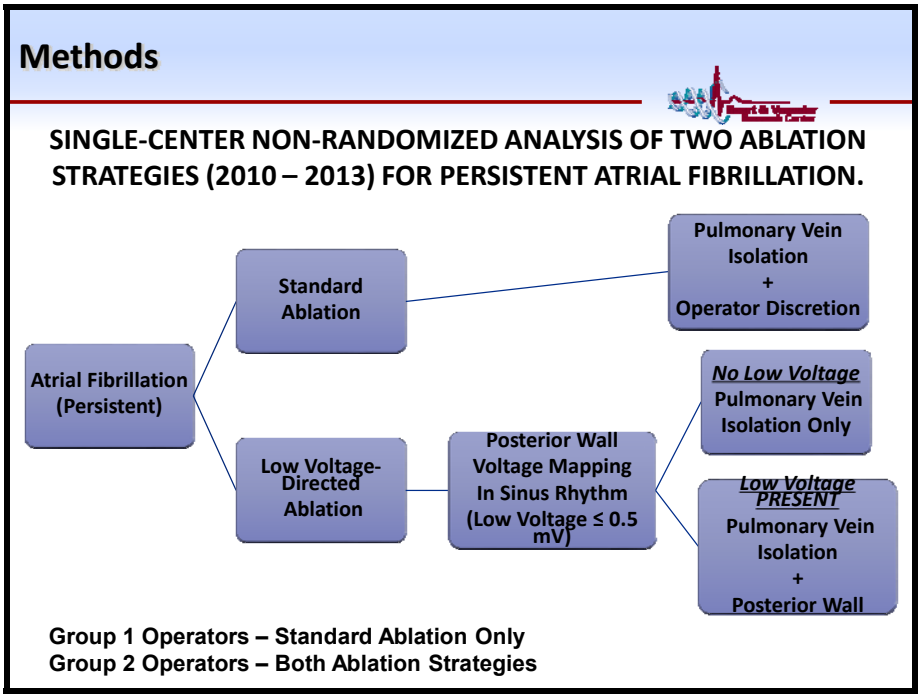

Figure 1

Low voltage mapping was performed with point-by-point mapping of the posterior left atrium and rendering to the anatomic shell of the left atrium and pulmonary veins. Low voltage diagnosis was made if the bipolar voltage was < 0.5 mV in the setting of adequate catheter tip-tissue contact and stability. Finding showed that in those patients randomized to the low voltage-directed cohort, 42% had posterior wall low voltage (Figure 2).

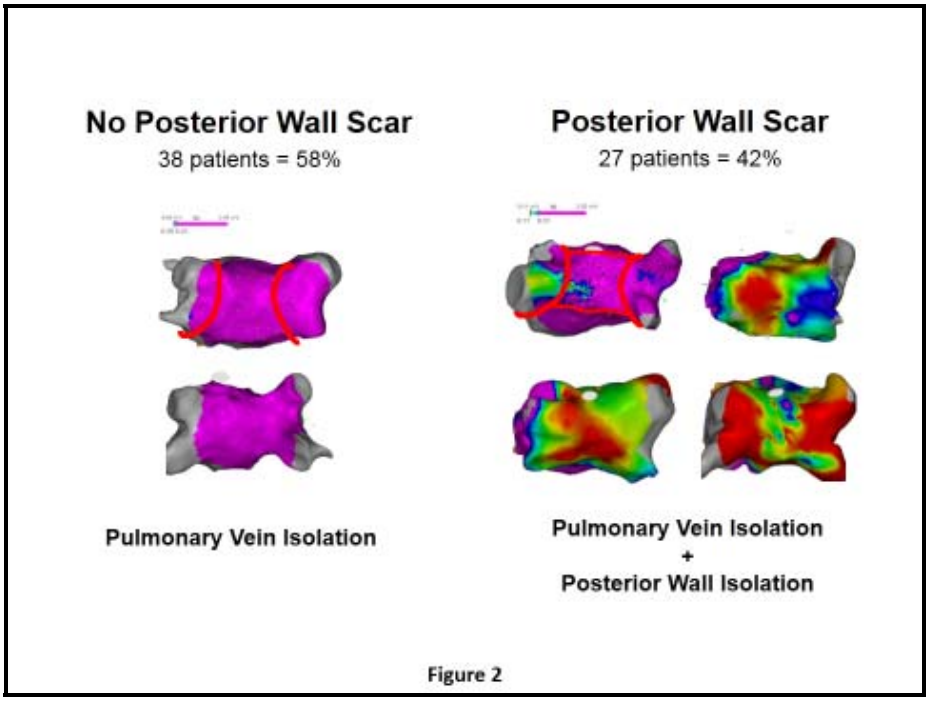

Figure 2

Patients were then followed for 1-year after their ablation with the primary endpoint of survival free of both atrial fibrillation and atrial tachycardia without the need for additional antiarrhythmic drugs. To this endpoint, the low voltage-directed approach improved 1-year arrhythmia free survival from 57% to 80% (p=0.005) (Figure 3).

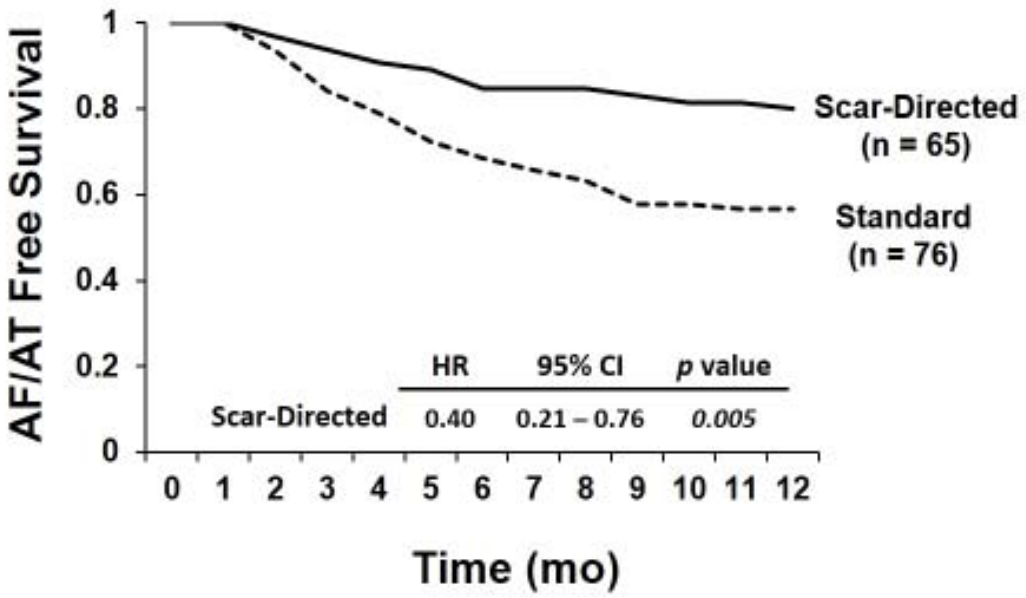

Figure 3

In subsequent multivariate analysis looking at all baseline and procedural characteristics, only a low voltage-directed ablation approach (HR 0.30, p=0.002) was associated with improved arrhythmia-free outcomes (Table 1).

	Hazard Ratio	95% CI	*p* value
Low Voltage-Directed	**0.30**	**0.14–0.64**	**0.002**
Posterior Wall Ablated	**0.74**	**0.30–1.85**	**0.53**
Posterior Wall Ablation using Box Technique	**1.71**	**0.29–9.99**	**0.55**
Demonstrated Posterior Exit Block	**0.48**	**0.10–2.41**	**0.37**
Time (performed Late vs. Early)	**0.92**	**0.49–1.74**	**0.81**

Group 2 Operator	**1.37**	**0.57–3.28**	**0.48**
LA Diameter	**1.40**	**0.83–2.35**	**0.21**
LVEF	**0.41**	**0.04–3.78**	**0.43**

Table 1

Several important insights were revealed from this pilot study that may help define ablation strategies, particularly in patients with more advanced subtypes of atrial fibrillation. First, the low voltage-directed approach improved 1-year arrhythmia free survival from 57% to 80%. The sustained improvement in outcomes after low voltage-directed posterior wall ablation confirms the feasibility of this approach and suggests the need for further study. Next, only the low voltage-directed approach was predictive of improved arrhythmia free survival. This finding highlights the need for understanding the atrial substrate as an independent variable to guide ablation. Finally, ablation of the posterior wall without regard to presence of absence of low voltage on the posterior wall was not a predictor of arrhythmia free survival. This latter insight highlights the need for upfront substrate mapping for low voltage to help define ablation approach rather than using a defined ablation paradigm based upon anatomy only.

After this pilot study there remain several questions. First, is point-by-point mapping adequate for in-vivo low voltage quantification? Second, although this study highlighted the importance of low voltage treatment along the posterior walls, it has been well documented that low voltage formation may involve all of the left atrium, particularly in those patients with fibrotic atrial cardiomyopathy. As such, is it possible to further improve outcomes by in-vivo low voltage mapping of the entire left atrium and using these obtained data to guide the ablation approach? Finally, what are the long-term impacts of low voltage-mediated ablation on left atrial function, stroke and heart failure risk, and quality-of-life?

However, the pilot study results support the hypothesis that using the presence or absence of low voltage as determined by electro-anatomical mapping to guide catheter ablation beyond pulmonary vein isolation (PVI) will improve atrial arrhythmia free survival in patients with persistent atrial fibrillation.

2.0 PROTOCOL DESIGN

2.1 Informed Consent:

The patient or legal representative must sign the most current Investigational Review Board approved informed consent form prior to enrollment.

2.2 Inclusion Criteria:

Subjects must meet all of the following criteria:

1. Non-Paroxysmal Atrial Fibrillation.
2. Failed or intolerable to at least 1 one antiarrhythmic drug (AAD).
3. 18-85 year of age at time of consent.
4. Able and willing to comply with all protocol visit requirements.
5. Signed Patient Informed Consent (ICF).

2.3 Exclusion Criteria:

Subjects will be excluded if any of the follow criteria are present:

1. History of prior left-sided catheter or surgical ablation for AF or atypical atrial flutter, including MAZE or mini MAZE.
   -Prior ablation for typical atrial flutter or left-sided ablation for WPW, AV node reentry tachycardia or focal ectopic atrial tachycardia may be included.
2. Uncontrolled heart Failure or NYHA Class IIIb or IV heart failure.
3. Ejection Fraction < 0.20
4. Left atrial size >60 mm diameter on echocardiogram
5. "Long standing" persistent AF defined as > or = to 1 year of continuous atrial fibrillation at the time of enrollment
6. Severe Pulmonary Hypertension (pp>70%)
7. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
8. Poor candidate for general anesthesia
9. Anticipated survival <1 year
10. MI or CABG within 3 months
11. Left atrial thrombus in pre-procedure imaging within 4 weeks of the procedure
12. Any documented thromboembolic event within 6 months.
13. Contraindication to anticoagulation.
14. Significant congenital anomaly or medical condition that may affect the integrity of study data.
15. Women who are pregnant (pregnancy test required if pre-menopausal or non-sterile)
16. Active enrollment in another investigational study involving a drug or device.

2.4 Randomization:

Patients that meet both inclusion and exclusion criteria will be randomized by the study clinical center. Patients will be randomized 1:1:1 into one of the following arms:

- PVI with additional total left atrial low voltage-directed ablation.
- PVI with posterior wall low voltage quantification and isolation

- PVI alone without low voltage quantification.

3.0 Pre-procedure

All patients will receive the best conventional medical therapy and anticoagulation use based upon HRS consensus recommendations taking into account their baseline risk factors for stroke. The need for interruption of anticoagulation and antiarrhythmic drug therapy for the procedure will be determined by the operator and their center guidelines.

The trial requires continuous monitoring for atrial arrhythmias. We will mandate the use of implantable loop recorders (ILR). The device will be under sterile conditions at the manufacture's recommended site on the precordium for arrhythmia monitoring. Implantation will occur between 1 month prior and 3 months post ablation since there will be a 3 month post ablation blanking period. If a dual chamber device is already present, implantation will not be required.

4.0 Intra-procedure

Prior to transseptal access, all patients will receive heparin with a goal ACT of 350-400 s. Double transeptal puncture is performed as usual per protocol of each site.

Arm 1: **(LD+PVI) PVI & Total Left Atrial Low voltage-Directed Ablation**. If the patient presents in atrial fibrillation, cardioversion will be performed to sinus rhythm. If the patient is still in atrial fibrillation, a synchronized cardioversion will be performed to allow low voltage mapping in sinus rhythm. Using an electroanatmical mapping system patients will undergo an initial voltage map of the *entire* left atrium with a multipolar recording catheter or circular mapping catheter during sinus rhythm. Any low voltage areas are then further assessed with detailed point by point voltage mapping with the ablation catheter. Low voltage will be defined as a location of >0.5x0.5cm that is reproducible with the contact force sensing catheter performed with documented contact force of >5g and <50g. Low voltage <0.5cm from a lesion will be considered a result of the actual lesion and will not be considered a low voltage region. An operator may choose to use the ablation catheter alone for mapping as long as the entire LA is adequately mapped (usually >50 points) evenly distributed along the septum, roof, posterior wall, and lateral wall of the left atrium. Adequate contact force should be achieved with each mapping point (minimum of 5g) with a contact force sensing catheter. Further ablation will be guided by the presence of left atrial low voltage and the relationship

to the pulmonary veins. Complete isolation of LA low voltage region will be performed and guided by electrical pacing parameters (Non-capture at 10mA or exit block demonstrated and documented). Wide area antral pulmonary vein isolation will also be performed with the endpoint of both entrance and exit block in the pulmonary veins. Isolation of the low voltage region will be left to the operator's discretion and may include widening the lesion set isolating the pulmonary veins to include the low voltage region or linear ablation to isolate the region. The presence of bidirectional block of the low voltage region will be tested. If bidirectional block is not achieved, additional ablation to achieve bidirectional block is at the direction of the operator and must be documented either way. However, if an isthmus is created by the low voltage isolation (1.5cm or less of viable atrial tissue) then further radiofrequency ablation will be performed to eliminate the isthmus. Patients who have atrial fibrillation recur before voltage mapping is completed will have ablation performed based on voltage data obtained and cardioversion repeated if needed with completion of voltage mapping of the entire LA. All low voltage regions are targeted for ablation in this manner. A 20 minute waiting period is required following isolation in each vein, following which each vein must be re-tested for isolation. If it has been found that the vein has reconnected, additional ablation must be performed to achieve isolation in that vein, followed by another 20 minute waiting period until isolation is seen. If isolation is not achieved, this must be documented and patients will be treated in the analysis in an intention-to-treat manner. High dose isuprel will be given up to 20 mcg/min for up to 10 minutes (at least an increase of ventricular rate >50% of baseline for 5 minutes is required). Additional triggers for atrial fibrillation will be pursued if the trigger causes sustained AF (AF for at least 30 seconds). In addition, if pulmonary vein reconnection is seen, then additional ablation to achieve pulmonary vein isolation will be pursued. A 20 minute waiting period is required before retesting with isuprel. If isuprel is not given, then this must be documented. Further ablation in this arm beyond the pulmonary veins, low voltage, and trigger ablation are to be avoided. Locations of frequent premature atrial complexes that due not induce sustained atrial arrhythmias under isuprel infusion should be avoided. Patients who receive further ablation not based on low voltage, pulmonary vein reconnection, or trigger ablation for sustained atrial arrhythmias will be treated in the analysis in an intention-to-treat manner. All additional ablation must be documented. Patients who do not receive isuprel or patients who did receive isuprel and pulmonary vein reconnection and/or AF triggers were not pursued will also be treated in an intention-to-treat manner. Testing for dormant pulmonary vein conduction with adenosine is discouraged. Patients will be will be treated in an intention-to-treat manner if additional ablation is pursued for patients on the basis of dormant conduction

Arm 2 (PW+PVI) PVI & Posterior Wall Ablation (not voltage directed): If the patient presents in atrial fibrillation, cardioversion will be performed to sinus rhythm. Voltage mapping will be performed in sinus rhythm. A voltage map will be performed of the *entire* left atrium, using the same voltage criteria, confirmation criteria, and mapping points as in arm 1. However ablation **will not** be guided by

low voltage quantification in the entire atrium or posterior wall. Instead, empiric isolation of the posterior wall will be performed in combination with wide antral pulmonary vein isolation. This may be performed as part of a "box" lesion set encompassing the posterior wall and both the left and right pulmonary vein antrums, or separate isolation performed at the operators' discretion. Waiting periods of at least 20 minutes following isolation are required for both pulmonary veins and posterior wall, including testing for bidirectional block in the posterior wall. Additional waiting periods of 20 minutes are required before re-testing the pulmonary veins or the posterior wall for bidirectional block following additional ablation to achieve isolation. Isuprel to test for triggers and reconnection will be given in the same manner as arm 1. Patients who receive further ablation not based on low voltage, pulmonary vein reconnection, or trigger ablation, or if isuprel was not given or given and triggers/reconnections were not pursued, will be treated in the analysis in an intention-to-treat manner.

Arm 3 (PVI alone-controls): If the patient remains in AF, cardioversion is performed into sinus rhythm as the other two arms. A voltage map of the *entire* left atrium is performed as in arms 1 & 2. However, ablation will not be guided by low voltage. Instead, wide area antral pulmonary vein isolation is initially performed with an electro-anatomical mapping system in the same manner as arms 1&2. Isoproterenol will be given and additional ablation performed as per the previous arms.

In all arms, additional ablation, including atrial flutter spontaneously occurring or induced during the procedure is discouraged but if done must be documented by the operator. Additional right atrial ablation, such as creation of a cavo-tricuspid isthmus line for atrial flutter or superior vena cava isolation, is also discouraged and if pursued, these patients will be treated in an intention-to-treat manner.

5.0 Post Procedure

One year follow-up is planned. Post procedure care is per standard of care with follow-up at 1 month, 3 months, 6 months, 9 months and 12 months. ECG at every follow-up is performed. Download of arrhythmia data will occur at each of these visits as well. We will use the typical post ablation blanking period for recurrence of atrial fibrillation of 3 months. Antiarrhythmic medications can be used during the typical "blanking period" of 3 months post procedure. But per protocol are stopped at 3 months post procedure (2 months post procedure in case of amiodarone). Re-initiation of an antiarrhythmic drug after 3 months will be considered a failure of primary endpoint of arrhythmia free survival. However, Anti-arrhythmic medication use after the blanking period for ventricular arrhythmias will not be included as an event. Anticoagulation is continued and monitored based on previous guidelines with use stratified by baseline stroke risk. A recording (CD) of the mapping during the procedure is to be obtained and retained for possible future analysis.

6.0 Objectives/Study Endpoints

The primary objective of this study is to demonstrate that low voltage mapping of the left atrium to guide additional ablation after wide area antral isolation of the pulmonary veins or posterior isolation in addition to pulmonary isolation will improve long-term outcomes with catheter-based radiofrequency ablation of the left atrium in patients with non-paroxysmal atrial fibrillation. All endpoints will be reviewed by a blinded adjudication committee.

6.1 Primary Endpoint

The primary endpoint is freedom from sustained or symptomatic atrial fibrillation, atrial flutter or atrial tachycardia (AF/AT) at 12 months. Recurrence of AF/AT excludes the 3 month blanking period. Sustained AF/AT is defined as >30 seconds as recorded on a monitoring device.

6.2 Primary Safety Endpoint

Safety as defined by the incidence of clinically significant Anticipated Adverse Events (AAEs) associated with the procedure. Clinical significance will be determined by a blinded adjudication committee.

6.3 Secondary Endpoints

1) Arrhythmia burden determined by the composite percent of atrial arrhythmia during the total time recorded on implantable monitoring devices.
2) Freedom from sustained AF/AT is defined as >30 seconds as recorded on a monitoring device.

7.0 Safety

Adverse events will be further defined as adverse events (AEs), serious adverse events (SAEs) and Anticipated Adverse Events (AAEs) as outlined below.

7.1 Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence in a subject receiving treatment. Any adverse event will be recorded on the respective patient's source/medical record.

All AE must be recorded in the source documentation and evaluated by the investigator to determine if clinically significant regardless of classification, seriousness, intensity, outcome or causality. If clinically significant, adverse events will be recorded on the case report forms by the investigator or study coordinator.

7.2 Serious Adverse Events (SAE)

A serious adverse event is an adverse event that:
• Led to a death.
• Led to a serious deterioration in the health of the subject that:
    a. Resulted in life threatening illness or injury.
    b. Resulted in a permanent impairment of a body structure or a body function.
    c. Required in-patient hospitalization or prolongation of existing hospitalization.
• Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
• Led to fetal distress, fetal death or a congenital abnormality or birth defect

7.3 Anticipated Adverse Events (AAEs)

Anticipated Adverse Events have been reported in association with ablation procedures. All anticipated adverse events occurring within 30 day of the study ablation are to be recorded for comparison between the 2 study arms. Atrio-esophogeal fistulas and PV stenosis are to be to be recorded through the 12 month follow-up visit. AAEs include:

a. All-cause mortality
b. Atrio-esophogeal fistula (through 12 mo)
c. Atrial perforation
d. Cardiac Tamponade
e. Pericardial Effusion
f. Pericarditis
g. Heart Block
h. Myocardial infarction
i. Cerebrovascular Accident (CVA)
j. Transient ischemic Attack
k. Thromboembolism
l. PV stenosis >70% from baseline (through 12 mo)
m. Diaphragm Paralysis
n. Pulmonary Edema
o. Pneumothorax
p. Limb Paralysis
q. Procedural blood loss ≥ 1000cc
r. Respiratory failure

7.4 Reporting of Adverse Events

The investigators at each of the participating sites are ultimately responsible for recording all adverse events in the source documentation. All adverse events are to be evaluated by the investigator to determine whether the events are clinically significant. The investigator should also determine whether the adverse event is related to the

device or procedure. All clinically significant adverse events are to be entered on the eCRFs at each visit and in a timely fashion so that the sponsor can review them in the EDC. The eCRFs for a given visit must report all reportable adverse events that occurred since the last documented visit.

8.0 Statistical Analysis

8.1 Power Calculation / Study Size:

In our pilot study, a Low voltage-Directed (LD) + PVI approach demonstrated a 1 year success rate of 80%, posterior wall isolation with pulmonary vein isolation showed a success rate of 64% and pulmonary vein isolation alone showed a 48% success rate. Based on this data, we assume the Low voltage-Directed approach and posterior wall isolation (PW)+ PVI to each have a 70% success rate and PVI alone arm to have a 50% success rate. We therefore made the following power calculation:

For each comparison of LD+PVI vs. PVI and PW+PVI vs. PVI
Probability of Type I Error (α) = 0.05
Power (1 - β) = 0.8
Survival Rate grp 1 = 0.7
Survival Rate grp 2 = 0.5
ratio (ssiz1 / ssiz2) = 1
Total sample size (both groups together, two tail model) required = 192 for comparisons
96 subjects in each of the 3 groups
288 subjects in total

We will use 4 sites, enrolling 4 patients/per site/month over 18 months.

8.2 Data Analysis Plan:

Primary and secondary outcomes will be analyzed using Kaplan Meier test. Cox proportional Hazards will be used to analyze primary outcome if baseline differences occur between the two arms in the study. The continuous variables will be reported as mean ± standard deviation (SD). The categorical variables will be reported as number of cases (n) and percentage. Comparison of characteristics across the groups will be performed using ANOVA for continuous variables and chi-square test for categorical variables. A two-tailed p value of <0.05 is considered statistically significant.

9.0 Schedule of Events

Required Testing	Screening	Baseline - Procedure	1 Month ± 2 weeks	3 Month[3] ± 2 weeks	6 Month ± 4 weeks	9 Month[4] ± 4 weeks	12 Month ± 4 weeks
Arrhythmia History	X						
Medical History	X		X	X	X	X	X
Demographics	X						
Randomization		X					
Pregnancy Exam[1]	X						
Left Atrial Thrombus Detection[2]		X					
Recording of procedure (CD)		X					
Physical Exam		X	X	X	X	X	X
Review of Cardiac Medications	X	X	X	X	X	X	X
Review of Adverse Events		X	X	X	X	X	X
ECG+ Arrhythmia download	X	X	X	X	X	X	X
ILR implantation	X	X	X	X			

1. required if of child bearing potential. 2. Required and according to institution standards.3. Discontinuation of AAD's required if clinically allowable. 4. If clinically indicated.

10.0 Monitoring:

Periodic monitoring will occur in order to verify data integrity. Monitoring visit will provide direct access to all source documentation necessary to verify the study data. All regulatory documentation will be maintained by each investigative site and made available to the monitoring team.

11.0 References:

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