PROSPECTIVE ELIMINATION OF DISTAL CORONARY SINUS-LEFT ATRIAL CONNECTIONS FOR ATRIAL FIBRILLATION ABLATION TRIAL: A RANDOMIZED, SINGLE BLIND, SINGLE CENTER STUDY

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Contents

Be sure to update the table of contents when you are finished creating your protocol. You can do this in Microsoft Word by going to the References section and clicking on the Table of Contents drop down menu.

List of Abbreviations

ACC: American College of Cardiology

AE: Adverse event

DMC: Data Monitoring Committee

DM: Diabetes Mellitus

ECG: Electrocardiogram

AF: Atrial Fibrillation

CS: Coronary Sinus

LA: Left atrial

Study Summary

Title	***Prospective Elimination Of Distal Coronary Sinus-Left Atrial Connections for Atrial Fibrillation Ablation Trial***
Short Title	*PRECAF Trial*
IRB Number	
Protocol Number	
Phase	**Pilot Study.**
Methodology	**Randomized; Single blind.**
Study Duration	**2 years**
Study Center(s)	**Single-center**
Objectives	**To examine the efficacy of targeting connections between coronary sinus and left atrium during an ablation procedure in addition to pulmonary vein (PV) isolation and non-PV triggers in Atrial fibrillation patients.**
Number of Subjects	**100 subjects are expected to be enrolled. An interim analysis will be performed after enrollment of 50 patients.**
Main Inclusion and Exclusion Criteria	**Inclusion criteria are:** ● **Patients with paroxysmal or persistent atrial fibrillation; AND** ● **Undergoing first AF ablation; AND** ● **Age ≥ 18 years.** **Patients are not eligible if they have any of the following exclusion criteria:** ● **Previous left atrial ablation;** ● **Women currently pregnant;** ● **Mental or physical inability to take part in the study;** ● **Known terminally ill patients.**

Investigational Product (drug, biologic, device, etc.)	
For Device include the planned use	*N/A*
For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment	*N/A*
Duration of administration (if applicable)	*N/A*
Reference therapy	*The reference therapy is pulmonary vein isolation and elimination of non-PV triggers. The investigational arm will include pulmonary vein isolation and non-PV trigger elimination, in addition to distal coronary sinus isolation.*
Statistical Methodology	**The primary efficacy analysis will be performed among the intent-to-treat study groups using Cox-regressions and Kaplan-Meier curves to compare time to the initial occurrence of AF after the blanking period following AF ablation.**
Safety Evaluations	**Occurrence of one or more of the following events during the 30 day period following the ablation procedure:** **1. stroke,** **2. myocardial infarction,** **3. esophageal injury,** **4. pulmonary vein stenosis,** **5. bleeding,** **6. heart failure, and** **7. death.**
Data and Safety Monitoring Plan	**Clinical data will be entered and securely stored** *The principal investigator will be responsible for monitoring the data quality and the ongoing safety of subjects.*

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including *Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.*

Introduction

1.1 Background and Relevant Literature

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of people in the US and around the world. Over the last 20 years, the catheter based AF ablation procedure has been widely adopted. However, the long-term success in paroxysmal AF is 50% and as low as 20% in persistent AF. To achieve temporary arrhythmia suppression, repeated ablation procedures may be needed. The cost of AF ablation among Medicare patients followed for a year after ablation was found to be US$16,049±$12,536 if ablation was successful versus US$19,997±$13,958 for failed ablation.[1] Previous literature indicates that most people have distal connections between coronary sinus musculature and the left atrium and that these connections may provide a substrate for single or multiple reentry beats as a trigger for atrial fibrillation.[2,3] In this proposal we wish to examine the efficacy of elimination of distal connection(s) between coronary sinus and left atrial musculature for suppression of recurrent atrial arrhythmias.

1.2 Name and Description of the Investigational Product

The reference therapy is pulmonary vein isolation and elimination of non-PV triggers. The investigational arm will include pulmonary vein isolation and non-PV trigger elimination, in addition to distal coronary sinus isolation. In the investigational group, distal coronary sinus pacing will be utilized to localize the earliest connection (aside from septal) from the coronary sinus to the left atrial musculature. Once localized focal radiofrequency lesions will be applied at the discretion of the investigator until central (septal) activation of the left atrium is noted during distal coronary sinus pacing.

1.2.1 Nonclinical Data

In canine hearts, the coronary sinus musculature is electrically connected to the right atrium (RA) and the left atrium (LA) which forms an RA-LA connection.[4]

1.2.2 Clinical Data to Date

In prior work, we sought to describe the prevalence and variability of coronary sinus (CS) and left atrial (LA) myocardium connections, their susceptibility to rate-dependent conduction block, and association with atrial fibrillation (AF) and flutter induction. The study cohort included 30 consecutive AF patients (age 63.3±10.5 years, 63% male). Multipolar catheters were positioned in the CS, high right atrium (HRA), and LA parallel to and near the CS. Trains of 10 pacing stimuli were delivered during sinus rhythm from each of the following sites: CS proximal (CSp), CS distal (CSd), LA septum (LAs), lateral LA (LAl), and HRA, at the following cycle lengths: 1000, 500, 400, 300, and 250 ms, while recording from the other catheters. With the CS 9 to 10 bipole just inside the CS ostium, CS-LA connections were observed in 100% at CS 9 to 10, 30% at CS 7 to 8, 23% at CS 5 to 6, 23% at CS 3 to 4, and 97% at CS 1 to 2. Eighteen patients (60%) had AF/atrial flutter induced. Rate-dependent conduction block of a CS-LA connection at cycle length of ≥250 ms was present in 17 (94%) of those with versus none of those without AF/atrial flutter induction (P<0.001). We concluded that rate-dependent eccentric CS-LA conduction block is associated with AF/atrial flutter induction in patients with drug-refractory AF undergoing ablation. The presence of dual muscular CS-LA connections, coupled with unidirectional block in one limb, seems to serve as a substrate for single or multiple reentry beats, and arrhythmia induction. (Huang, D. et al. Association of Rate-Dependent

Conduction Block Between Eccentric Coronary Sinus to Left Atrial Connections With Inducible Atrial Fibrillation and Flutter. Circ Arrhythm Electrophysiol. 2017 Jan;10(1)).

Importantly, 4 patients in the above study cohort, with AF/AFL induction after rate-dependent CS–LA conduction block, the connection site was targeted from the endocardial LA surface. These were distal CS to lateral LA connections. The CS–LA connection was successfully and safely ablated in all 4 cases. Repeating the identical pacing protocol after ablation failed to induce any arrhythmia in these cases (Circ Arrhythm Electrophysiol. 2017 Jan;10(1)).

1.2.2.1 Human Pharmacokinetics

N/A

1.2.2.2 Clinical Studies in Adults

The study will enroll only adults patients aged > 18 years.

1.2.3 Clinical Studies in Children

No children will be enrolled in this study.

1.3 Dose Rationale (if applicable)

N/A

2 Study Objectives

2.1 Primary Objective

To examine the efficacy of targeting connections between coronary sinus and left atrium during an ablation procedure in addition to standard pulmonary vein (PV) isolation and non-PV triggers elimination.

3 Investigational Plan

3.1 General Design

The study is designed as a randomized, single-blind, small scale pilot study. Expected duration of subject participation is six months. A 30-day event monitor will be used for the first month after ablation. Then, regular clinic visits at 6 weeks and 6 months will arranged after ablation with 12 lead electrocardiogram check-up. In the last month, a 30-day event monitor will be set to detect the recurrence of atrial arrhythmias.

3.1.1 Screening Phase

Participants with be recruited in the cardiology clinic at the Hospital of the University of Pennsylvania or satellite sites. The protocol will be explained to those who are indicated for atrial fibrillation ablation. Eligible participants will be identified according to the inclusion/exclusion criteria section of the protocol. Written consent will be obtained before the ablation procedure .

3.1.2 Study Intervention Phase

Participants will be randomized in a 1:1 fashion to 2 groups. Group 1 participants will undergo the current standard of care ablation with pulmonary vein isolation and non-pulmonary vein triggers elimination; group 2 participants will undergo coronary sinus-left atrium connection ablation, in addition to pulmonary vein isolation and non-pulmonary vein triggers. The distal coronary sinus electrode pair will be paced at an output not higher than 10mA. During pacing, the earliest activation time in the left atrium at 20 plus milliseconds after the pacing spike will be localized and targeted for ablation. Lesions will be delivered at 40 watt or less, for 30 seconds or less and titrated down using standard criteria at the discretion of the proceduralist. Stimulation for induction of AF with pacing cycle length from 250 to 180 ms or 2:1 capture

will be performed from proximal coronary sinus and distal coronary sinus and at the site of left atrial to CS connection before and after ablation.

3.1.3 *Follow Up Phase*

A 30-day event monitor will be used for the first month after ablation. Then, regular clinic visits at 6 weeks and 6 months will arranged after ablation with 12 lead electrocardiogram check-up. In the last month, a 30-day event monitor will be set to detect the recurrence of atrial arrhythmias. An adjudication committee consisting of two electrophysiologists that are blinded to the randomization scheme will review AF events. Time to first AF episode will be recorded as the primary outcome.

3.1.4 Allocation to Interventional Group

Study randomization will be performed in a 1:1 fashion using the Urn Randomization program (https://health.uconn.edu/community-medicine/programs/health-services-research-unit/project-match/urn-randomization/) while balancing sex and AF type (paroxysmal and non-paroxysmal). The master list of study assignments will be kept by the study coordinator in a password protected and encrypted computer.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint of the study is the recurrence of atrial arrhythmia post-ablation. The primary endpoint is defined as a non-self-terminating bout of atrial fibrillation, atrial flutter, or atrial tachycardia >30 seconds in duration following the 90-day post-ablation blanking period.

3.2.2 Secondary Study Endpoints

AF burden will be compared among study groups as a secondary outcome variable. AF burden will be measured from the 30 day monitors.

3.2.3 Primary Safety Endpoints [if applicable]

The primary safety *composite* outcome is defined by occurrence of one or more of the following events during the 30-day period following the ablation procedure: stroke, myocardial infarction, esophageal damage, pulmonary vein stenosis, bleeding, heart failure and death.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

- Patients with paroxysmal or persistent atrial fibrillation; AND
- Undergoing first AF ablation; AND
- Age ≥ 18 years.

4.2 Exclusion Criteria

- Previous AF ablation
- Women currently pregnant;
- Mental or physical inability to take part in the study;
- Known terminally ill patients.

4.3 Subject Recruitment

Participants with be recruited from investigator clinical practices in the University of Pennsylvania Health System.

4.4 Duration of Study Participation

Participants will be part of the study for 6 months after ablation.

4.5 Total Number of Subjects and Sites

Recruitment will end when 100 participants are enrolled at Penn.

4.6 Vulnerable Populations:

Vulnerable populations will not be targeted.

5 Study Intervention

5.1 Description

The reference therapy is pulmonary vein isolation and elimination of non-PV triggers. The investigational arm will include pulmonary vein isolation and non-PV trigger elimination, in addition to distal coronary sinus isolation.

5.2 Intervention Regimen

In the investigational group, distal coronary sinus pacing will be utilized to localize the earliest connection (aside from septal) from the coronary sinus to the left atrial musculature. Once localized focal radiofrequency lesions will be applied at the discretion of the investigator until central (septal) activation of the left atrium is noted during distal coronary sinus pacing.

5.3 Receipt

N/A.

5.4 Storage

N/A

5.5 Preparation and Packaging

N/A.

5.6 Blinding

The unblinded research coordinator will keep a master file of participant assignments. Once a participant is randomized, the investigator/clinician for the patient will be notified of the participant assignment. The remainder of the research team and the participant will be blinded to participant assignment.

5.7 Administration and Accountability

N/A.

5.7.1 Return or Destruction of Investigational Product

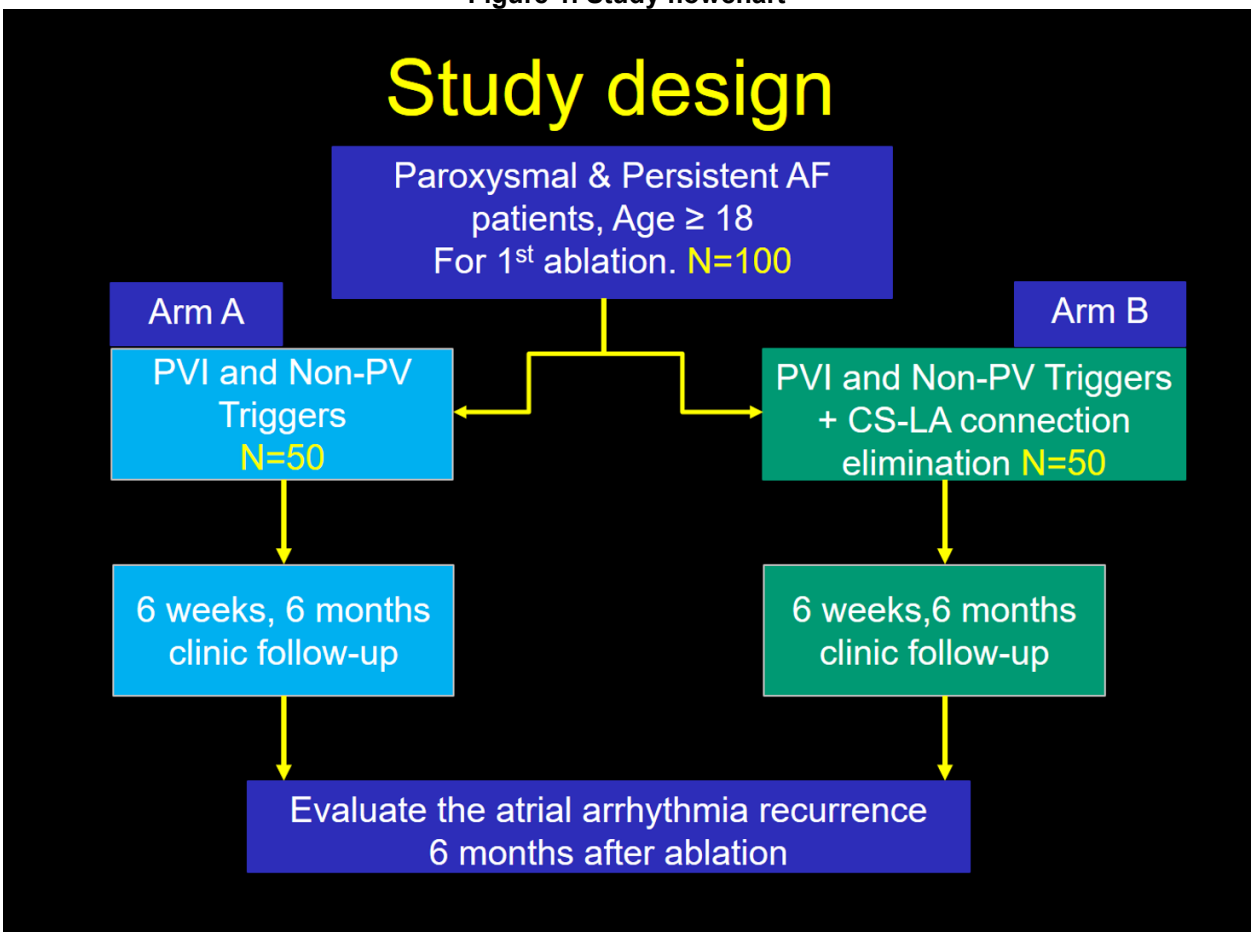
N/A.

6 Study Procedures

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Intervention: Ablation**		
Visit Number			**Visit 1**	**Visit 2**
Study Days		**0**	**6 weeks**	**6 months**
Informed Consent/Assent	X			
Review Inclusion/Exclusion Criteria	X			
Demographics/Medical History	X			
Physical Examination	X		X	X
Vital Signs: BP, HR, RR	X	X	X	X
Height and Weight	X	X		
Randomization		X		
Adverse Event / Unanticipated Problems Assessment		X	X	X
12-Lead ECG	X	X	X	X
30-day Monitor		X		X

Figure 1. Study flowchart



6.1 Study Intervention Phase

6.1.1 Baseline visit

- Physical Exam
- Vital Signs
- Height and Weight
- Medical Records Review
- Review Inclusion/Exclusion Criteria
- Informed consent

6.2 Follow Up Phase of the Study

6.2.1 Visit 1 (6 weeks)

- Physical Exam
- Vital Signs
- Medical Records Review
- Assess possible adverse events
- Consider stopping anti-arrhythmic drug if continued post procedure
- 12 lead ECG

6.2.2 Visit 2 – End of Study Visit (6 months)

- Physical Exam
- Vital Signs
- Medical Records Review
- Assess possible adverse events
- 30 day monitor
- 12 lead ECG

6.3 Unscheduled Visits

Subjects may experience unanticipated problems, complications or intolerable symptoms such as palpitations, dyspnea after ablation, unscheduled visits may occur. Physical examination, 12-lead ECG, medical treatment, and complication management may be applied for the study subjects. If subjects have severe condition, admission will be arranged.

6.4 Subject Withdrawal

Participants may be withdrawn if failure to adhere to protocol requirements is noted, or if the participant wishes to and consents to withdrawal.

7 Study Evaluations and Measurements

7.1 Medical Record Review

The following variables will be abstracted from the medical chart:

- *Date of birth*
- *Height*
- *Weight*

- *History of co-morbidities related to AF including obstructive sleep apnea, hypertension, and thyroid disroders.*

- *Any history of prior cardiovascular disease*

- *Cardiovascular imaging details including echocardiography, CT angiography, or cardiovascular MR imaging*

7.2 Physical Examination

Standard cardiovascular physical examinations will be performed at study enrollment, on the date of ablation and during the 2 follow-up visits.

7.3 Vital Signs

Standard vital signs at clinic visits ill be recorded. No study related changes to routine measurements will be made.

7.4 Laboratory Evaluations

N/A

7.5 Efficacy Evaluations

12 lead ECGs obtained at clinic visits, and as prompted by symptoms, as well 30 day monitors immediately following AF ablation and at 6 months will be utilized for efficacy assessment. Two electrophysiologists that will be blinded to study assignments will adjudicate the AF ECG data. Time to first AF episode (following ablation) and AF burden (following ablation) will be ascertained.

7.6 Safety Evaluations

Comparing study adverse outcomes between the two study groups will be utilized to assess the safety of the additional ablation lesions in the investigational arm.

8 Statistical Plan

8.1 Primary Endpoint

The primary endpoint is the recurrence of atrial arrhythmia post-ablation. The primary endpoint is defined as a non-self-terminating (>30 seconds) episode of atrial fibrillation, atrial flutter, or atrial tachycardia demonstrated by ECG or 30 day monitors after the 90-day post-ablation blanking period.

8.2 Secondary Endpoints

The secondary endpoint will be AF burden on the immediate post ablation and 6-month 30-day monitors.

8.3 Sample Size and Power Determination

Assuming alpha 0.05, power 0.80, and 1:1 randomization of 100 participants, and 0.7 probability of AF freedom in the control group, we will resolve a 2-sided minimum experimental arm hazard ratio of 0.2 with implementation of the log-rank test.

8.4 Statistical Methods

Descriptive summaries of baseline clinical and demographic characteristics will be provided by randomized treatment assignment for each analysis population. Cumulative incidence curves for the first atrial arrhythmia recurrence will be constructed by randomization group and compared via log rank and proportional hazard models.

8.4.1 Baseline Data

Baseline and demographic continuous variables will be summarized as mean+standard deviation (SD). Categorical variables will be expressed as standard percentages.

8.4.2 Efficacy Analysis

Cumulative incidence curves for the first atrial arrhythmia recurrence and for death will be constructed by randomization group and compared using log rank and proportional hazard methods.

8.4.3 Safety Analysis

All subjects entered into the study and randomized at the baseline visit will have detailed information collected on adverse events for the overall study safety analysis

8.5 Subject Population(s) for Analysis

Data from all participants that are randomized into the study will be analyzed as long as the participants does not withdraw from the study.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

*An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of study procedures will be considered to be adverse events if the abnormality:*

- *results in study withdrawal*
- *is associated with a serious adverse event*
- *is associated with clinical signs or symptoms*
- *leads to additional treatment or to further diagnostic tests*
- *is considered by the investigator to be of clinical significance*

Additionally, any untoward medical occurrence associated with ablation near the coronary sinus will be considered an adverse effect.

9.1.2 Serious Adverse Event

Serious Adverse Event

*Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:*

- *fatal*
- *life-threatening*
- *requires or prolongs hospital stay*
- *results in persistent or significant disability or incapacity*
- *an important medical event*

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

*All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.*

9.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report

form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, but grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

The principal investigator will characterize the relationship of each adverse event to the study procedures as definitely related, probably related, possibly related, unlikely or unrelated.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. The minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9.4.2 Investigator Reporting: Notifying the Penn IRB

Any adverse events will immediately be reported to the Penn IRB using forms and guidelines at https://irb.upenn.edu/reportable-event.

9.5 Unblinding Procedures

We do not anticipate any medically necessary situation for which the participant must be unblended regarding their randomization assignment.

9.6 Stopping Rules

N/A

9.7 Medical Monitoring

The Principal Investigator will oversee the safety of the study along with other co-investigators. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

9.7.1 Data and Safety Monitoring Plan

- Principal Investigator monitoring

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Study data will be collected from the EMR and investigator clinic notes. Data will be de-identified prior to recording into the study database.

- *MS Excel will be used to maintain an ongoing database*
- *The study coordinator will have access to PHI*
- *Data containing PHI will be kept on a password protected computer in the PI research laboratory*
- *Data will be stored for 1 year following study completion and publication*

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

N/A

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be

made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Risks

The risks for subjects are the same as standard ablation in atrial fibrillation with the exception of slightly prolonged mapping and ablation time by approximately 5-10%. Ablation of the region near the coronary sinus is also associated with higher risk of coronary injury. However, the risk of coronary injury is low given the investigators prior extensive experience ablating in this region for peri mitral flutters and accessory pathways.

12.2 Benefits

Subjects may benefit from the intervention with longer atrial arrhythmia free duration, the study also provide the potential beneficial ablation strategy in addition to standard ablation in atrial fibrillation.

12.3 Risk Benefit Assessment

The risks of participating in the study are likely outweighed by the potential benefits of participating in the study.

12.4 Informed Consent Process / HIPAA Authorization

The risks and benefits of the procedure will be delineated by investigators, and consent will be obtained before ablation either in clinic or in the Cardiology Recovery Unit.

- *The study PI or a co-investigator will obtain consent*
- *Privacy will be assured by de-identification of all data in the study database.*
- *Subjects will be permitted to provide consent at the time of the consent discussion*
- *Investigators will explain the study associated risks and benefits and consent process in eight grade language to ensure that subjects comprehend the nature of the study*
- *It will be made clear that study participation is not necessary*
- *Written informed consent will be documented and informed consent documentation will be retained in the the PI laboratory*

13 Study Finances

13.1 Funding Source

N/A – pilot study

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

N/A

14 Publication Plan

Study results will be presented in de-identified format at national meetings and published in peer reviewed journals.

15 References

Bibliography

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[3] Association of Rate-Dependent Conduction Block Between Eccentric Coronary Sinus to Left Atrial Connections With Inducible Atrial Fibrillation and Flutter. Dong Huang, et al. (Circ Arrhythm Electrophysiol. 2017;10:e004637. DOI: 10.1161/CIRCEP.116.004637.)

[4] Electrical Conduction Between the Right Atrium and the Left Atrium via the Musculature of the Coronary Sinus. Matthias Antz et al. (Circulation. 1998;98:1790-1795.)