PROTOCOL TITLE:

Mapping Electrogram Morphology Recurrence for Atrial Fibrillation Ablation

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1.0 Objectives

The overall goal of this early feasibility project is to test the feasibility and safety of performing real-time electrogram morphology recurrence (EMR) mapping in patients with persistent atrial fibrillation (AF) to locate areas of high electrogram morphology recurrence rate. We believe that the EMR mapping can be integrated into cardiac mapping and used to identify potential sites for ablation. Furthermore, this study could provide preliminary data on the efficacy of this technology's ability to terminate or slow AF.

We will test this technology on ten subjects undergoing a second ablation procedure. We will map the AF utilizing the EMR to indicate locations of stable activity. This information will be provided to the cardiac electrophysiologist performing the procedure to integrate with the other electroanatomic data to develop an ablation strategy focused on ablating the drivers for AF. By targeting these drivers, we hypothesize that we can produce acute AF termination or AF cycle length prolongation. In addition to testing the real-time electrogram morphology recurrence mapping, we would also like to determine the acute effects of radiofrequency ablation of areas of high recurrence rates and determine long term freedom from AF following ablation of areas of high recurrence rates.

2.0 Background

Atrial fibrillation (AF) (an abnormal, rapid heart rhythm coming from the upper chambers of the heart [atria]) is the most common type of heart rhythm disorder or arrhythmia (abnormal heart rhythm). Instead of the heart beating in a steady pattern, in AF the upper chambers of the heart (atria) quiver rapidly in an unsteady manner. Atrial fibrillation may be treated with drug therapy designed to either prevent the heart rate from going too fast during atrial fibrillation (rate control therapy) or with drug therapy designed to stop the abnormal rhythm and maintain normal heart beating (rhythm control therapy). Atrial fibrillation may also be treated with catheters inserted into blood vessels that can be placed inside the heart to eliminate the critical zones or triggers for atrial fibrillation or stop those conditions that keep it going (catheter ablation). It is not known how to best locate these critical zones or triggers to be targeted by catheter ablation.

The aim of this study is to investigate a recently developed electrogram mapping technique for AF, known as an electrogram morphology recurrence (EMR) analysis. This technique identifies areas of the atria that have high rates of electrogram morphology repeatability that may be characteristic of AF sources. This non-linear technique uses cross-correlation of AF activation waveforms to determine the frequency of the most common waveform morphology. In a pilot study of patients who underwent ablation targeting the PVs, electrograms with highest recurrence rates located in the left atrium predicted ablation success. In contrast, having these fast/repeatable electrograms in the right atrium indicated a very poor ablation (performed in the left atrium) success rate (0%). Additionally, in a canine rapid atrial pacing model of AF, EMR was able to identify AF rotors. Although these preliminary studies suggest that areas of high rates of EMR may play a role in AF persistence, it is unknown if mapping of these sites can be used to direct treatment (i.e. ablation).

3.0 Inclusion and Exclusion Criteria

Approximately fifteen (15) subjects will be recruited from the University of Miami. Patients will be screened for participation in this study by the investigator or his clinical staff for inclusion. The study aims to complete ten (10) participants through the ablation procedure and a minimum of one (1) year follow-up.

INCLUSION CRITERIA:

- Male and female, at least 21 years of age
- Subjects with persistent AF with one prior failed ablation for persistent or long standing persistent AF

EXCLUSION CRITERIA:

- Inability to sign consent.
- Patients with a life expectancy <1 year.
- Patients with chronic kidney disease with sufficiently low GFR that precludes either CT angiogram of the heart or contrast MRI study.
- Patients with contraindications to catheter ablation for atrial fibrillation (i.e. left atrial thrombus, class IV heart failure, etc)
- Pregnant women and women that are breast feeding
- Patients with multiple (2 or more) prior failed ablations.
- Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

4.0 Study-Wide Number of Subjects

Not applicable, this study is not a multicenter study.

5.0 Study-Wide Recruitment Methods

Not applicable, this study is not a multicenter study.

6.0 Multi-Site Research

Not applicable, as this is not a multicenter study.

7.0 Study Timelines

The research subjects will be undergoing a clinically-indicated second ablation procedure. On the day of the ablation procedure, the procedure will be utilizing the new mapping technology to identify areas of high EMR and this information will be incorporated into the ablation strategy in conjunction with the other electroanatomic data. As is the usual

clinical routine, patients will be followed every 3-12 months after completion of (or early withdrawal from) study treatment, as clinically indicated, for a minimum of one year.

Upon completion of all study data collection on the 10 participants, primary data analysis will begin.

Follow-up. The patients will undergo standard post ablation follow-up as part of their routine clinical care. As per the Heart Rhythm Society guidelines, following ablation, patients receive some type of post ablation monitoring (Event monitor, Holter monitor, smartphone monitor, Implantable loop recorder-LINQ). This choice of monitoring will be made by the patient's physician in conjunction with the patient based on clinical need. The follow-up schedule will also be determined based on patient and clinical need, and the guidelines. The following table presents an idealized version of the follow-up schedule, but this will be adjusted based on clinical need.

	Screening	Day 0	5-28 days post	2-4 months post	4-8 [3] months	10-14 months
H&P	X	X	X	X	X	X
ECG	X	X	X	X	X	X
Labs	X[4]	X[5]				
Monitoring[1]					X	X
Device Interogation[2]	X	X	X	X	X	X

1 Monitoring information will be collected if ordered for standard clinical care. This includes Ambulatory monitoring (Holter), Event Monitor, SmartPhone Monitor
2 Device Interrogation will be performed as part of standard clinical care. This includes implantable loop recorder (LINQ), pacer or defibrillator, if the patient has a device
3 If a patient does not have an office visit in this window, a phone follow-up will be obtained.
4 Labs are clinically indicated and include basic metabolic panel for screening
5 Labs are clinically indicated and include basic metabolic panel, CBC and coagulation panel and may be performed within 3 weeks prior to the procedure

8.0 Study Endpoints

Feasibility of performing real-time electrogram morphology recurrence maps will be determined to assess if maps show specific areas of high morphology recurrence.

The acute effects of ablation will be classified as either causing AF termination, AF slowing, or no change. We will identify the number of subjects in each category.

In addition, we will collect 30 day safety endpoints that may occur after the ablation using the following Table and then categorize whether the AE/SAE is related to the procedure.

Adverse Events during or attributable to the Ablation Procedure

TYPE OF AE	Grade	Attribution categories
Adverse Event vs. SAE • cardiac perforation • cardiac tamponade • Vascular • Pulmonary • Proarrhythmia • Phrenic nerve paralysis (lasting > 24 hours) • Pulmonary Vein Stenosis • GI bleed • CVA • TIA • MI • Infection • Allergic reaction during procedure • CHF • Syncope/near syncope • GI/Esophageal complications	Mild (grade 1): the event causes discomfort without disruption of normal daily activities. Moderate (grade 2): the event causes discomfort that affects normal daily activities. Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status. Life-threatening (grade 4): the patient was at risk of death at the time of the event. Fatal (grade 5): the event caused death	Definite – The AE *is clearly related* to the study. Probable – The AE *is likely related* to the study. Possible – The AE *may be related* to the study treatment. Probably unrelated- The AE is likely not related to the study Unrelated – The AE *is clearly NOT related* to the study.

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- ***Results in death.***

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- ***Is life-threatening.***

The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- ***Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.***
- ***Results in persistent or significant disability or incapacity.***
- ***Is an important medical event***

9.0 Procedures Involved

Screening/Baseline

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not

exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

The screening procedures include:

- Informed Consent
- Medical history: Complete medical and surgical history
- Demographics: Age, gender, race, ethnicity
- Review subject eligibility criteria
- Review previous and concomitant medications
- Physical exam including vital signs (temperature, pulse, respirations, blood pressure), height and weight
- Pregnancy test (for females of child bearing potential).

Procedures During Treatment

Prior to Treatment

- Physical exam, vital signs
- Hematology
- Cardiac MRI or Cardiac CT Angio for left atrial and pulmonary vein anatomy
- Echocardiogram
- Left atrial thrombus will be ruled out by either transesophageal echocardiogram or Cardiac CT
- Antiarrhythmic drug therapy will be guided by the managing physician.

Ablation study

- Anesthesia – type determined by clinical factors
- Catheter insertion
- Procedural anticoagulation – intravenous heparin to maintain ACT>300 sec
- Mapping
- Ablation, as per MD operator
- Electrical cardioversion (if necessary)
- Adjunctive ablation procedure monitoring (i.e. adequacy of lesion generation, esophageal temperature monitoring, and phrenic nerve monitoring) will be employed as determined by the MD operator based on clinical needs

Follow-Up Procedures

Patients will remain on anticoagulation for a minimum of two months after the procedure. Further anticoagulation will be determined by the managing physician.

Approximately 30-90 days after ablation:

- Physical exam, vital signs
- ECG

Every 3 months:
Patients will be followed every 3-12 months, as clinically indicated, after completion of (or early withdrawal from) study treatment, for a minimum of one year.

- ECG
- Event monitoring per clinical guidelines

MRI (to be performed only if CTA is not already done)

The MRI will be performed prior to the ablation as standard of care to delineate pulmonary vein anatomy prior to the ablation procedure. The study will utilize data from this scan. This exam requires contrast-enhancement.

Subjects may receive Magnevist, Multihance, or Ablavar depending on their kidney function and the discretion of the radiology staff. Contrast will be given as follows:

- **For subjects with a GFR > 60 ml/min:**
  A total dose of 0.2 mmol/kg Magnevist or Multihance or a total dose of 0.03 mmol/kg Ablavar will be injected intravenously as the contrast agent.
- **For subjects with a GFR 30-60 ml/min:**
  A total dose of 0.1 mmol/kg Multihance or Magnevist or a total dose of 0.03 mmol/kg Ablavar will be injected intravenously as the contrast agent.
- **Subjects with a GFR <30 ml/min will either be excluded from this study or undergo MRI without contrast agent.**

The contrast dye will be injected intravenously at 1 ml/s, followed by 20 ml of saline flush at 1 ml/s. The scan will begin 4 seconds after first arrival of contrast in the pulmonary veins. Our researchers will utilize the data collected from the MRI to calculate atrial wall stress. Approximately 15 minutes after injection of contrast, the subjects will undergo the delayed enhancement MRI protocol. There will be an additional approximately 15 minutes of advanced sequences added to the MRI for evaluation of the atria.

The EMR/Ablation Phase

Fifteen second AF recordings will be made using a multipolar electrode catheter to map the entire right atrium and then the left atrium. Additional recordings will be made from the coronary sinus using a standard multielectrode catheter. A Lasso catheter (10 electrodes, 9 bipoles) may be used to record electrograms from the pulmonary veins, superior vena cava, and right and left atrial appendages. The 3D location of each electrogram will be documented using a commercially available 3-D mapping system (such as Carto 3, Biosense Webster, Diamond Bar, CA). Recurrence plot maps will be created using the EMR mapping software. Additional electrograms will be recorded and analyzed near sites of high recurrence based on the initial maps. We estimate an additional 20-30 minutes per atrium for the creation of the maps.

Candidate AF sources will be identified using the recurrence plot maps and maps of recurrence cycle length in conjunction with the other electroanatomic data. Radiofrequency ablation will be guided by the EMR maps. If ablation does not cause termination, the atria

will be remapped a second time to determine if another potential source still exists. If so, additional ablation will be performed at that site. After ablation based on the morphology recurrence plot, if AF has not terminated, *physician discretion will determine whether further EMR mapping guided ablation or* further "standard" ablation will be performed as per physician protocol. AF termination will be diagnosed if either sinus rhythm is restored with ablation or a regular atrial tachycardia or flutter ensues. Stable coronary sinus recordings will be used to assess ablation-induced slowing using the real-time software. The 3-D position of each ablation lesion will be documented.

10.0 Data and Specimen Banking

No biological specimens will be collected or stored for this research.

The data that will be stored includes demographic/clinical information on the research subject and the data from the EMR protocol. Please see section 11 for more information on the length of storage, location, access, etc. Any data requests from outside parties may also be submitted via written request to the PI and all data will be de-identified prior to release.

11.0 Data Management

Data Analysis

Clinical Data: Demographic and clinical data will be tabulated as means and standard deviations for continuous variables and counts with percentages for categorical variables.

For EMR Data: We will compare the cycle length prolongation seen with EMR ablation to that seen in a cohort of age and sex matched patients selected from our database of patients who have undergone a second AF ablation procedure for persistent AF with conventional methods. We will also compare acute termination rates and procedure duration. A difference of 10% in cycle length slowing between recurrence-based ablation vs. conventional ablation can be detected with 10 patients per group with 0.89 power. We will define a successful Phase I as AF termination or cycle length slowing of the coronary sinus of at least 15% in at least 7 of 10 patients from morphology recurrence mapping directed ablation.

Data Confidentiality

Stored data will include demographic/clinical information on the research subject and the data from the EMR. When possible, coded identifiers will be utilized to minimize the risk for breach of confidentiality. The PI, sub-I's, and other authorized personnel will be granted access to coded identifier lists as necessary to complete study objectives. Hard copies of paper and/or digital data will be stored in locked, limited access areas in the offices of the Cardiovascular Division, University of Miami, located on the 11th floor of the Clinical Research Building. Access to these areas is limited to authorized personnel. Electronic records will be stored in password-protected computer systems that will be accessible to authorized personnel only. Any data sent outside of the University of Miami

will be de-identified prior to release.

Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms, signed patient HIPAA authorizations). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Records related to this research study will be retained for the amount of time required by Federal regulations and ICH Good Clinical Practice, but no less than 6 years after the end of the study.

The PI and/or sub-I's may publish the results of this study in conjunction with appropriate scientific and medical personnel. However, data presented in published materials will not contain identifiers linking that data back to subjects. Patient name, DOB, or other elements constituting protected health information will be stripped from any data, image, etc. before publication or presentation.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

12.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study procedures for the changes observed; or
- death.

12.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom,

or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

12.1.2 Severity of Adverse Events

The severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

12.1.3 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- ***Results in death.***
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- ***Is life-threatening.***
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect**
- **Is an important medical event**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

12.1.4 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the current Investigator's Brochure

12.1.5 Reporting Requirements for Adverse Events

Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the ablation or within 30 days of the ablation.
- The IRB and FDA must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

Routine Reporting

- All other adverse events - such as those that are expected, or are unlikely or definitely not related to the study participation - are to be reported annually as part of regular data submission.

12.2 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, the IRB must be notified within five (5) business days of making the change.

Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).

- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Study personnel should report protocol violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

12.3 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.4 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with the Code of Federal Regulations, Good Clinical Practice and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13.0 Withdrawal of Subjects

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- During the mapping and ablation procedure, if the patient is not deemed sufficiently stable to perform the research mapping procedure;
- Patient is unable to comply with protocol requirements;
- Patient experiences toxicity that makes continuation in the protocol unsafe;

- Treating physician judges continuation on the study would not be in the patient's best interest;
- Lost to follow-up. Example language: If a research subject cannot be located to document survival after a period of 1 year, the subject may be considered "lost to follow-up." All attempts to contact the subject during the one years must be documented.

14.0 Risks to Subjects

The general risks related to participation in this study are predominantly those related to standard ablation therapy which the patient would be exposed to even if he/she proceeds with ablation without participating in this study. There is a risk of death with any serious complication related to ablation therapy that does not respond to emergency treatment.

This study involves the following risks related to the insertion or placement of catheters, the use of medications needed for the ablation procedure, moving the catheters in the heart, or delivery of energy inside of the heart.

The insertion of the catheters into the leg veins or arteries can be accompanied by the following:

- The possibility of infection, bleeding, bruising, pain or blood clot formation under the skin. A blood clot can develop in one of the veins in the leg or even in the lungs. A vein or artery could be injured and may require surgery for repair.
- Development of a bladder or kidney infection, infection elsewhere in the blood, pneumonia or fluid in the lung.
- The possibility of air entering the blood stream.

Medications given during the procedure can also have side effects:

- X-ray (Fluoroscopy) used to visualize the heart and veins may cause a skin rash. If dye is given, this can also damage the kidneys.
- The dye and anesthetic drug may produce an allergic response leading to a skin rash, a drop in blood pressure, or difficulty breathing. If this occurs, a ventilator will be used and the procedure can be continued. In rare cases, pneumonia could develop.
- The blood thinner, heparin, or similar drug could cause bleeding anywhere in the body.
- Nausea or a visual migraine-like headache.

Other procedure risks are related to positioning catheters within the heart:

- The most serious of these is heart muscle perforation by a catheter. In many cases the hole created by the catheter seals when the catheter is removed.
- In some cases, bleeding into the sac surrounding the heart could result in a drop in blood pressure. In such cases, a needle and catheter tube may be inserted from a position underneath the breastbone or between the ribs to drain this blood. In rare cases, open-chest surgery may be required.
- Moving the catheters within the heart could damage a heart valve, which could require surgical repair or replacement.
- A heart attack or stroke could also occur.

- An artery around the heart may spasm, develop a blood clot, or be damaged.
- There is also a possibility that the normal electrical system could be damaged, making a pacemaker necessary.
- The X-rays used to guide catheter placement could cause skin burns, or in the long run result in some form of cancer, or damage to the heart or lungs.
- Pacemaker leads could be disturbed or the pacemaker damaged, making repair or replacement necessary.

The final group of risks has to do with the actual ablation:

- Chest pain could be experienced when the energy is delivered, or inflammation around the heart may cause chest pain after the procedure.
- In addition, energy delivery on the left side of the heart could lead to blood clot formation, cause a stroke, or other organ damage.
- With energy delivery, there is also a slight increase in the chance of a heart attack, or the development of an atrial esophageal fistula. This can produce severe infection or a severe stroke, both of which may cause death.
- Ablation in or near a vein can also damage the vein itself.
- In a low percentage of cases, a pulmonary vein can be narrowed or significant scarring may occur, which can cause permanent lung damage. In some cases, an angioplasty (balloon) procedure may be required to open up this narrowing or scarring with a balloon catheter. In other cases, a coil or "stent" may be required to keep the vessel open. If the vessel re-narrows after the stent is placed, a repeat catheter procedure on more than one occasion could be required. Under rare circumstances open-heart or lung surgery could be required to correct the narrowing or scarring. In most cases, this can be dealt with successfully, although the consequences could be serious or cause death.
- There is a possibility of damage to one of the nerves around the heart. In rare cases, a nerve supplying the diaphragm (the muscle that helps with breathing) may become sufficiently damaged to cause the diaphragm to be paralyzed (unable to move). This is unlikely to be serious, and the muscle function usually returns over the course of 4 to 16 months, although sufficient damage could lead to permanent diaphragm paralysis.
- There may be elevated temperatures or abnormal blood tests.

It is possible that AF may return following the catheter ablation procedure requiring medication therapy, one or more additional ablations, or the rhythm may become worse. Overall, from the clinical portion of the ablation procedure, the risk of a serious complication is between 2-3%. The risk of a minor problem is approximately 5%.

The specific risks related to this study relate to the potential lengthening of the procedure due to additional mapping and the possibility that the sites identified by the EMR mapping for ablation do not lead to successful ablation of the AF.

Confidentiality: Patient confidentiality is an important issue in any clinical research study. All stored data will be de-identified using established protocols. Subject's names will not be used in publications or data analyses nor will they be available for discussion by any investigators other than the treating physicians.

15.0 Potential Benefits to Subjects

The possible benefits to the subjects from this study may include fewer or no more episodes of atrial fibrillation and reduction or elimination of AF-related medication. In cases where participation in this study does not improve AF and its symptoms, the information that is learned from this study may benefit other people with AF and may advance medical understanding of arrhythmias.

16.0 Vulnerable Populations

Not applicable, no vulnerable populations to be enrolled in this study.

17.0 Multi-Site Research

Not applicable, not a multi-site study.

18.0 Community-Based Participatory Research

Not applicable.

19.0 Sharing of Results with Subjects

The research subjects will not be given the results of the research. The subjects may be given results of their personal findings at the discretion of the treating Cardiac Electrophysiologist.

20.0 Setting

Subjects will be recruited at the University of Miami Hospital and the Cardiovascular Multispecialty Clinic. The ablation procedure and EMR recordings will be performed in the Cardiac Catheterization Lab at the University of Miami Hospital.

21.0 Resources Available

This study will involve the recruitment of up to fifteen (15) subjects with AF with one prior failed ablation. Patients undergoing a second catheter ablation procedure based on clinical guidelines (as determined by patient and his/her physician) will be considered for this study. Patients with persistent AF (as defined per the most recent guidelines) will be considered for this project. Subjects will be recruited from the medical center environment using standard techniques.

All of the critical facilities/resources needed for the success of this project are available to the PI and research staff. The PI is responsible for delegating study-related tasks to the appropriate personnel for the purposes of this study. Personnel, including sub-I's, and with oversight from the PI, are expected to abide by all laws, regulations, and policies enforced

by the aforementioned entities. All personnel involved in this study will have successfully completed institutional training for human-subjects protections (e.g. CITI Training).

22.0 Prior Approvals

Not applicable.

23.0 Recruitment Methods

Subjects undergoing a second ablation procedure will be recruited from patients at the University of Miami. Investigators and/or study coordinators will approach the patients, explain the protocol, and ascertain whether they would be interested in participating, and prospective subjects will be provided with a copy of the approved informed consent for review.

The research subjects will not be financially compensated for participation in the study.

24.0 Local Number of Subjects

Approximately fifteen (15) subjects will be enrolled in this study and screened for participation in this study. Ten (10) participants found eligible for the trial will receive the ablation procedure and then will be followed every 3-12 months, as clinically indicated, after completion of (or early withdrawal from) study treatment, for a minimum of one (1) year. These ten patients will be matched with a cohort of age and sex matched patients who have undergone a second AF ablation procedure for persistent AF with conventional methods.

25.0 Confidentiality

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Data used for reports or publications will never include identifiable information such as name, date of birth, social security number, address, or medical record number and in most cases will not include any identifiers other than sex, age, race, and diagnosis.

26.0 Provisions to Protect the Privacy Interests of Subjects

The subject's main contact will be their personal electrophysiologist. Outside of their personal physician the research and clinical staff have years of experience in clinical settings and have completed CITI training to ensure that the research subject will be comfortable. The subject's direct contact with research staff will be limited, as the research protocols will be completed in the clinical setting with the clinical staff.

The Principal Investigator (PI) is responsible for personally conducting or supervising the conduct of human-subjects research and for protecting the rights, safety, and welfare of the subjects enrolled in the research. The PI must ensure that all human-subjects research is

conducted in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and requirements or determinations by other regulatory entities

A participant's privacy and confidentiality will be respected throughout the study. When possible, coded identifiers will be utilized to minimize the risk for breach of confidentiality. The PI, sub-I's, and other authorized personnel will be granted access to coded identifier lists as necessary to complete study objectives. Study records will be stored as described in section 10.0 of this protocol.

27.0 Compensation for Research-Related Injury

The research in this study is part of a clinical procedure the subject elected to undergo, therefore research related injuries will not be compensated. The following language will be included in the consent form to explain what to do in the event of a research-related injury.

> "If you become ill or get an injury or illness as a result of study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.
>
> The University of Miami has no program to pay for medical care for research-related injury. The hospital and researchers will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome."

28.0 Economic Burden to Subjects

Only patients who have decided to undergo radiofrequency ablation for treatment of their atrial fibrillation will be enrolled. All pre-procedure testing, procedural costs, and clinical visits/evaluations are standard of care and are therefore the responsibility of the patient and his/her insurer. There will be no additional charges to the patient or costs associated with the research portion (specifically the new EMR mapping) of the procedure. As the research procedures involve a little bit of extra time for tests/procedures that are being done anyway, there will be no additional costs for this from the professional or technical side.

29.0 Consent Process

Potential subjects will be identified by clinical physicians at the University of Miami and informed about the details and significance of this study. Investigators and/or study coordinators will approach the patients, explain the protocol, and ascertain whether they would be interested in participating, and prospective subjects will be provided with a copy of the approved informed consent for review. If a potential subject is interested in enrolling, informed consent and HIPAA authorization will be obtained from the subject by personnel involved in the study. Signed informed consent will be administered and HIPAA

authorization obtained either at the potential subject's clinic visit or prior to the ablation procedure.

Prospective subjects may speak languages other than English. Spanish-speaking subjects will be consented with a certified Spanish translation of the consent form. Prospective subjects who speak languages other than English or Spanish will be consented using a qualified translator to translate the English document and a translated short form of the consent in their own language.

A waiver of consent and waiver of HIPAA will be requested for matched historical control subjects. Patients in the historical control group will not undergo any research procedures; their standard of care clinical data will be used retrospectively as a comparison group to the research participants. The minimum necessary protected health information will be collected from the records of the matched historical control subjects. Only essential information will be taken from their medical records in order to ensure comparability with enrolled subjects; study team members will not contact these control subjects. The information will be stored in locked areas in the research offices of the Cardiovascular Division and password-protected computers; only personnel involved in the research will have access. Because these subjects will be historical controls and their information would be taken from medical records, it would be difficult to obtain consent and HIPAA authorizations from this group prior to reviewing their records.

30.0 Process to Document Consent in Writing

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required. Once this essential information has been provided to the patient, all questions have been answered, and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

31.0 Drugs or Devices

Device used in this trial consists of a software FDA approved as a Category B1 Device
IDE # G160216 under the name of Morphology Recurrence Plot Mapping software