Left Atrial Anatomy Reconstruction Using Model Based Fast Anatomical Mapping
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NCT03349476
Dovument Date: Nov 20, 2020



# Advanced Model Based Fast Anatomical Mapping Software for Atrial Fibrillation Ablation
# IDE 170110

# MFAM 2

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**Icahn School of Medicine at Mount Sinai**
**New York, NY**

**Version 3.2**
**NOVEMBER, 2020**

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**PROTOCOL SUMMARY**

| | |
|---|---|
| **Title:** | **Advanced Model Based Fast Anatomical Mapping Software for Atrial Fibrillation Ablation (mFAM-2)** |
| **Objective:** | This prospective, multicenter observational study will examine:<br>1) The accuracy of left atrial anatomy reconstruction using updated mFAM software<br>2) The left atrial geometry creation time<br>3) Fluoroscopy time for left atrial anatomy creation |
| **Design:** | This is a prospective, multi-center, non-randomized observational trial. The total enrollment will be up to 150 patients. |
| **Enrollment:** | Eligible subjects will be consented for participation in the trial prior to undergoing first-time ablation for atrial fibrillation. Patients are considered eligible if they meet the following criteria:<br>1. Age ≥ 18 years<br>2. Have either paroxysmal, persistent, or longstanding persistent AF, which are defined as follows:<br>1) Paroxysmal AF – episodes of AF lasting < 7 days and terminate without electrical or pharmacologic cardioversion<br>2) Persistent AF – episodes of sustained AF > 7 days, or episodes of AF which are terminated by electrical or pharmacologic cardioversion after ≥ 48 hours.<br>3) Longstanding persistent AF – episodes of AF lasting longer than one year.<br>3. Are planned to undergo a first catheter ablation procedure for AF (prior ablation for typical atrial flutter or supraventricular tachycardia is allowed)<br>4. Have the ability to understand the requirements of the study and sign the informed consent form.<br>5. Are willing to adhere to study restrictions and comply with all post-procedural follow-up requirements<br><br>Patients will be excluded from the trial if they have:<br>1. Rheumatic heart disease,<br>2. Current intra-cardiac thrombus,<br>3. Class IV HF,<br>4. Unable to sign consent<br>5. Unstable angina<br>6. Recent cerebral ischemic events<br>7. Contradiction to anticoagulation<br>8. Recent cardiac surgery (CABG or valve replacement within 6 months)<br>9. Complex congenital heart disease<br><br>Patients are considered enrolled once consented. Patients who do not undergo AF ablation within 90 days of enrollment will be considered to be screen failures.<br><br>Up to 150 subjects are expected to be enrolled in the study. |

| | |
|---|---|
| **Clinical Sites:** | 1. Mount Sinai Hospital, New York, NY<br>2. Grandview Medical Center, Birmingham, AL<br>3. Naples Community Hospital, Naples, FL<br>4. Cleveland Clinic, Cleveland, OH |
| **Time Course:** | Expected duration of patient enrollment is approximately 6 months to 1 year. |
| **Subject Description:** | Subjects will only be eligible for this study if they are ≥ 18 years of age, have a history of AF, and are planned for AF ablation |
| **Endpoints:** | 1. Accuracy of map (defined as the distance between the acquired points and the surface of the left atrial geometry)<br>2. Left atrial geometry creation time<br>3. Total Fluoroscopy time (for sites that use fluoroscopy) |
| **Follow-Up** | Until hospital discharge |
| **Study Sponser:** | Vivek Reddy , M.D.<br>Icahn School of Medicine at Mount Sinai<br>One Gustave L Levy Place, Box 1030<br>New York, NY 10029, USA |
| **Site, Monitoring, and Data Management Center** | Electrophysiology Clinical Research Group<br>Icahn School of Medicine at Mount Sinai<br>One Gustave L Levy Place, Box 1030<br>New York, NY 10029, USA |

## 1 CONTACT INFORMATION

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### 1.1 STUDY SITES & INVESTIGATORS

| Site | Principal Investigator |
|---|---|
| 1. Mount Sinai Hospital | Mohit Turagam, MD |
| 2. Grandview Medical Center | Jose Osorio, MD |
| 3. Naples Community Hospital | Dinesh Sharma, MD |
| 4. Cleveland Clinic | Oussama Wazni, MD |

## 2 STUDY OBJECTIVE

This prospective, multicenter observational study will examine the ability of model based fast anatomical mapping (mFAM) with additional software modifications to create left atrial (LA) geometry and guide atrial fibrillation ablation.

Specifically, the study will assess the following issues in atrial fibrillation ablation:

1) The accuracy of left atrial anatomy reconstruction, defined as the distance between the acquired points and the surface of the left atrial geometry.
2) Left atrial geometry creation time
3) Fluoroscopy time for left atrial anatomy creation, for those sites which use fluoroscopy

We hypothesize that this approach will lead to accurate LA geometry creation for AF ablation more rapidly than standard techniques without a significant increase in fluoroscopy time.

## 3 INTRODUCTION, RATIONALE AND BACKGROUND

Atrial fibrillation (AF) ablation for paroxysmal and persistent atrial fibrillation typically involves pulmonary vein isolation (PVI) with left atrial endocardial ablation. With a radiofrequency (RF) ablation approach, the left atrial geometry can be defined using electroanatomical mapping systems. Reconstruction of left atrial geometry using the CARTO3 system (Biosense Webster, Diamond Bar, CA) is currently performed using a multielectrode mapping catheter that is localized in 3D space utilizing magnetic- and impedance-based technologies with a functionality called FAM (fast anatomical mapping). An alternative approach to creation of left atrial geometry using a novel technique based on a library of previously defined left atrial archetypes – called "mFAM" – has been studied in this investigator-initiated FDA IDE protocol..

mFAM applies a model based approach for reconstruction of left atrial chamber anatomy. The model created by fitting a parametric shape model to the point cloud acquired by a catheter. The model includes a geometrical primitive for each of the pulmonary veins, the left atrial appendage, the left atrial chamber, and the mitral valve (as seen in Figure 1-A). The geometrical primitives are blended to form the left atrial structure (as seen Figure 1-B).

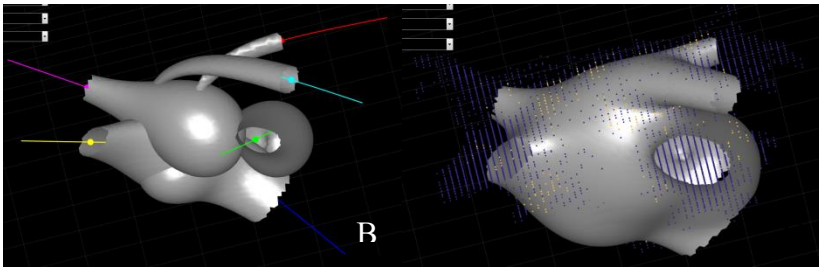



*Figure 1: A: Model components. B: Blended model, superimposed on all catheter points' samples (blue), and locations where the catheter was in contact with the surface (yellow).*

A set of more than 200 atrial CT scans were used to initially develop and train this model and define relevant proportions and sizes for "realistic" and anatomically accurate left atria. Examples of these features are: the angle between the PVs, distances from atria center to the mitral valve and pulmonary vein ostia, and the ratio of these values to left atrial volume. This approach provides a way to represent the most probable left atrial geometry with limited information.

This anatomy could be adapted to more accurately represent clinically important points. For points of importance, such as ablation sites, the model deforms to align with the location when there is contact while keeping proportion and sizes congruent with the existing defined anatomical information (as seen in Figure 2).

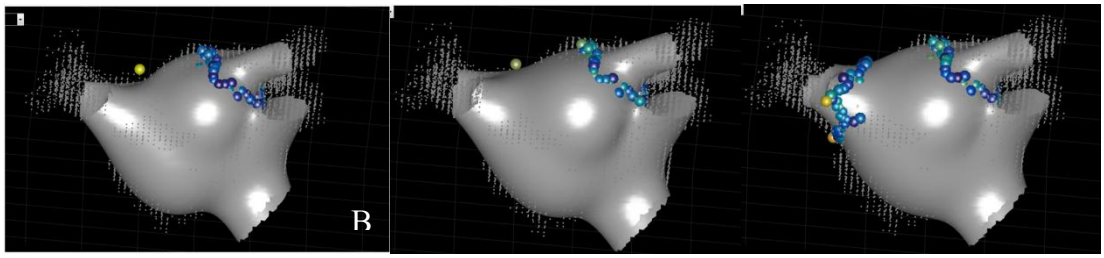



*Figure 2: A: Model with original catheter points (gray dots), left side ablation points (blue spheres), first right side ablation point (yellow sphere). B: Adaptation of the model to first right side ablation point. C: Final model, adapted to right side ablation points.*

This model-based fast anatomical mapping strategy has proven feasible in retrospective analyses, and the anatomy has been validated in a pilot study of 21 patients with anatomy in the left atrium collected with a force-sensing catheter. Distance between the mFAM generated anatomy and the reference anatomy was further improved when Navistar data was added to it (see Figure 3). In the current trial, mFAM has been used prospectively to reconstruct left atrial geometry reconstruction for AF ablation procedures..

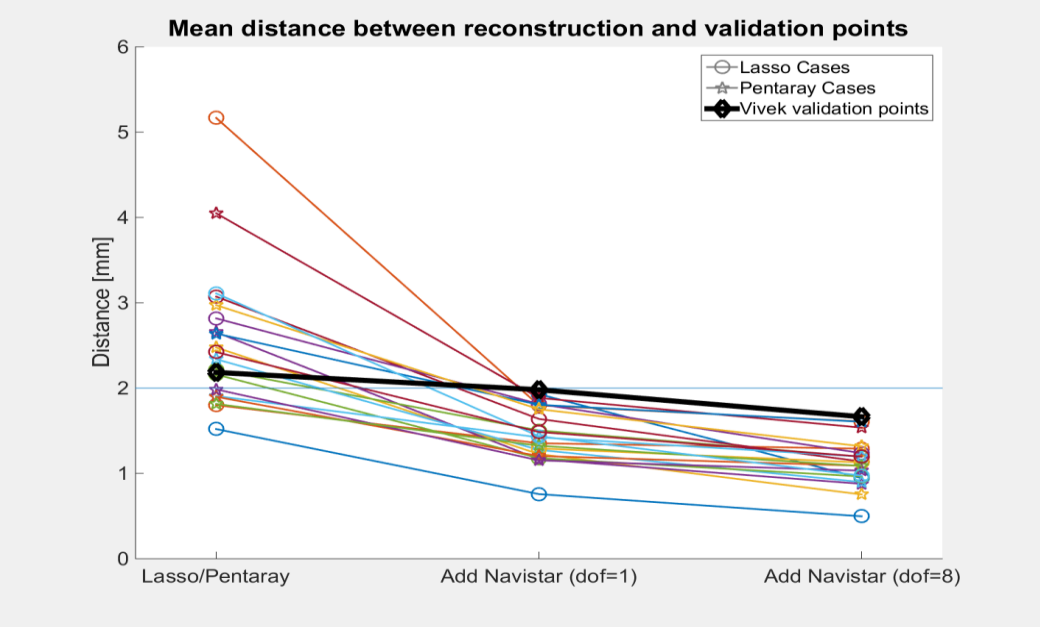



*Figure 3: Validation results on a pilot study of 21 patients using a Lasso/Pentaray alone or with Navistar data with 5-10 grams of force. With addition of the Navistar data, distance to reconstruction < 2mm.*

In this protocol amendment, we propose expanding enrollment in this multi-center, non-randomized study to evaluate additional improvements on this software solution to guide AF ablation.

**Overview of mFAM and Software Improvements**

The mFAM Workstation is a computerized system used to reconstruct the shape of the left atrium of the heart by fitting a parametric shape model to points data which is obtained by conventional electrophysiological methods acquired by a catheter. The mFAM Workstation uses recorded catheter positions and other data inputs collected using conventional multi-electrode catheters and, using proprietary software algorithms, it generates output data files that are displayed as a 3D anatomic structure.

mFAM improves on the FAM functionality by applying a model-based approach for reconstruction of left atrial chamber anatomy. This approach was tested in the patients initially enrolled in this trial for reconstruction of the left atrial geometry for AF ablation. Since that time, additional software modifications have been made to help to improve accuracy and efficiency of left atrial mapping and ablation during AF ablation procedures. Specifically, the following software enhancements/algorithms have been added:

1. Mechanical Tissue Proximity Indication (mTPI): allows for automatic acquisition of points from a standard multi-electrode catheter. The system uses mechanical deformation properties of the catheter to determine tissue contact.

2. Enhanced Catheter Stability: allows for estimation of catheter stability throughout the respiratory cycle instead of only end-expiration by accounting for real-time respiratory motion during measurement of catheter location.

3. Improvements to the proprietary mFAM algorithm, which applies a model-based approach to reconstruct left atrial geometry.

4. SoundFAM: incorporates ultrasound frames captured with a standard intracardiac ultrasound catheter (Soundstar, Biosense Webster, Diamond Bar, CA) into the model-based reconstruction of left atrial geometry. This feature also allows for 3D reconstruction of the location of the esophagus to determine its relationship to the left atrium, which is critical for AF ablation procedures.

The available results from clinical use in the current IDE trial and from cases done in the EU are listed in Figure 4. Over 98% of all points and 100% of magnet points were located less than 3mm from the recreated left atrial surface.

| Data set | Contact Points | | | | Magnets | | | | Number of valid time points | Number of valid cases |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean Distance | | RMS Distance | | Mean Distance | | RMS Distance | | | |
| | Mean | % <3mm | Mean value | % <4mm | Mean value | % <3mm | Mean value | % <4mm | | |
| All Cases | 1.54 | 98.4% (370/376) | 2.54 | 93.09% (350/376) | 0.89 | 100% (376/376) | 1.23 | 100% (376/376) | 376 | 119 |
| IDE | 1.5 | 98.66% (147/149) | 2.56 | 91.28% (136/149) | 0.8 | 100% (149/149) | 1.1 | 100% (149/149) | 149 | 50 |

*Figure 4: Data from all cases performed with mFAM software and the cases performed thus far in the current IDE trial*

## 4. DEVICES, SOFTWARE AND PROCEDURES

### 4.1 MFAM Workstation

The mFAM Workstation operates in direct interface with the CARTO® 3 System V7 workstation. Coordination between the Workstation and the CARTO® 3 System includes:

- Automatic import of data recordings (such as position, respiration, and force) from the CARTO® 3 System
- Analysis of data by proprietary software algorithms
- Transfer of the 3D anatomical structure to the CARTO® 3 System
- Display of the 3D anatomical structure on the monitor of the CARTO® 3 System
- The maps can be superimposed over original 3D maps and the real-time position of the mapping catheter in the CARTO® 3 System.

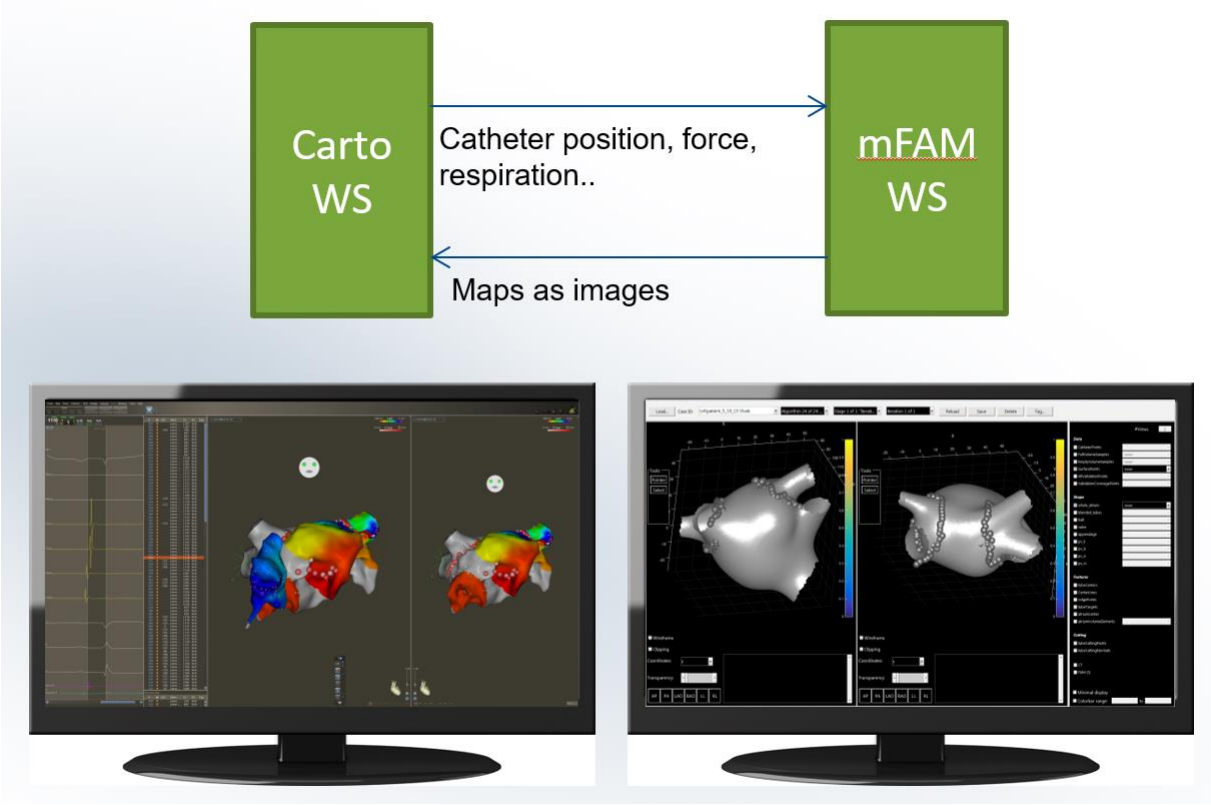



*Figure 5: Real time data is acquired by placing the catheter into pulmonary veins and is transferred to the mFAM workstation, where it is processed, and the image maps are transferred back to the CARTO workstation.*

**4.2 Ablation catheters:**

The AF ablation procedure will be performed using any of the following marketed catheters: (Note: the ablation catheters listed below are FDA approved for the treatment of paroxysmal atrial fibrillation but not persistent.)

- Biosense ThermoCool SmartTouch SurroundFlow (STSF) ablation catheter
- Biosense ThermoCool SmartTouch (ST) ablation catheter

## 5 SCHEDULE OF TREATMENT AND TESTS

**TABLE 1: SCHEDULE OF TREATMENTS AND TESTS:**

| | Baseline | Procedure | Discharge |
|---|---|---|---|
| **Type of visit** | Office | Hospital | |
| **Informed Consent** | X | | |
| **Brief History & Physical** | X | | |
| **CT or MRI** | X | | |
| **Echo** | X | | |
| **EKG** | X | | |
| **Medications** | X | X | X |
| **Adverse Events** | | X | X |

## 6 ENDPOINTS

**PRIMARY CLINICAL ENDPOINTS**

1. Accuracy of map (defined as the distance between the ablation points and the surface of the mFAM geometry)
2. Left atrial geometry creation time
3. Fluoroscopy time

## 7 STUDY SUBJECTS

### 7.1 INCLUSION CRITERIA

1. Age ≥ 18 years
2. Have either paroxysmal, persistent, or longstanding persistent AF, which are defined as follows:
   a) Paroxysmal AF – episodes of AF lasting < 7 days and terminate without electrical or pharmacologic cardioversion
   b) Persistent AF – episodes of sustained AF > 7 days, or episodes of AF which are terminated by electrical or pharmacologic cardioversion after ≥ 48 hours.
   c) Longstanding persistent AF – episodes of AF lasting longer than one year.
3. Planned to undergo first catheter ablation procedure (prior ablation for typical atrial flutter or supraventricular tachycardia is allowed)
4. Ability to understand the requirements of the study and sign the informed consent form.
5. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements

### 7.2 EXCLUSION CRITERIA

1. Rheumatic heart disease
2. Current intra-cardiac thrombus
3. Class IV HF
4. Unable to sign consent
5. Unstable angina
6. Recent cerebral ischemic events
7. Contradiction to anticoagulation
8. Recent cardiac surgery (CABG or valve replacement within 6 months)
9. Complex congenital heart disease

## 8 SAMPLE SIZE

This safety and efficacy study will enroll up to 150 patients across 4 US centers. This number has been determined on the basis of study feasibility and not by statistical means. This is a feasibility study of the study software in which the sample size of the clinical investigation is intended to provide preliminary assessment of safety and performance.

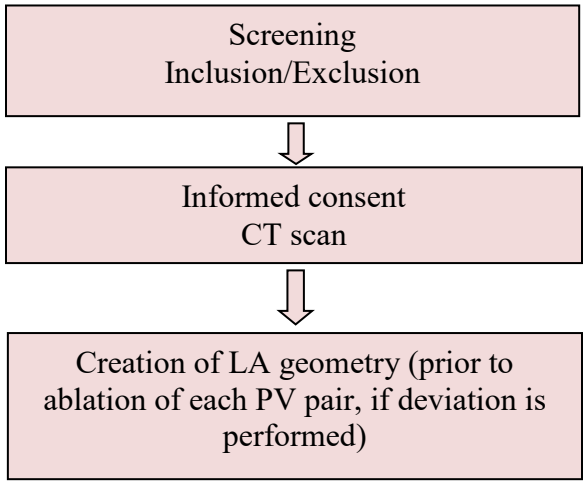
## 9 PATIENT ENROLLMENT AND WITHDRAWAL

Patients meeting the study inclusion criteria will be identified in the outpatient or inpatient setting by investigators. Patients will be followed by one of the study site primary or co-investigators.

The study will typically be described (including the risks and benefits) during the initial clinic or hospital

visit. Consent will typically be obtained at the time of the initial assessment if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be encouraged to take a copy of the consent form home to contemplate whether he/she would like to be enrolled in the study (see Appendix 1 for informed consent form.) Only patients who voluntarily provide consent will be included in this study. Consent will be obtained prior to undergoing the ablation procedure. Patients will be able to withdraw from the study at any point without compromising their medical care. All data will be de-identified and protected in accordance with institutional and HIPAA guidelines, including 1) de-identification of all geographic subdivisions smaller than a state; 2) all elements of dates related to the individual; 3) telephone and fax numbers; 4) email addresses; 5) social security, medical record, health plan beneficiary, account, and certificate/license numbers; 6) vehicle identifiers; 7) device identifiers; 8) URLs and IP addresses; 9) biometric identifiers; and 10) photographic images.

Eligible subjects will be consented for participation in the trial prior to undergoing AF ablation. Patients are considered enrolled once consented. Patients who do not undergo ablation within 90 days of enrollment will be considered to be screen failures. Patients will only be followed until hospital discharge.



# 10 STUDY PROCEDURES

## 10.1. PRE-PROCEDURE EVALUATION

Patients will be consented for the study in either the inpatient or outpatient setting. The following tests and procedures will occur before the ablation as a routine part of pre-procedural medical assessment:

- Recording of patient medical history (including details of previous ablation)
- Recording medication history (including all anti-arrhythmic drugs used and duration of use)
- Obtain β-HCG in females of child bearing age the morning of the procedure as per usual clinical practice
- Collect any pre-procedural echocardiograms
- Consent must be obtained before the procedure.

## 10.2 PRE-PROCEDURE MEDICATION MANAGEMENT

In preparation for the catheter ablation procedures, continuation of anticoagulation medication will be strongly encouraged per the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.

For patients who present for their procedure in atrial fibrillation and who have not received therapeutic anticoagulation for at least three weeks prior to the procedure, evaluation of the left atrial appendage with pre-procedural transesophageal echocardiogram or intra-procedural intracardiac echocardiogram will be required.

## 10.3 PROCEDURAL DETAILS

- Patients will be brought to the electrophysiology laboratory in a fasting state
  - Patients will have transseptal access with administration of anticoagulation to achieve activated clotting time of at least 300 seconds at the time of the initial left atrial ablation lesions. If esophageal deviation is planned, it will be performed prior to creation of left atrial geometry and ablation of the target vein pair.
- The CARTO3 mapping system and mFAM software will be used to create left atrial geometry and ablation will be performed to isolate pulmonary veins as per standard practice.
  - If esophageal deviation was performed, after completion of one PV vein pair the esophagus will be deviated again and a new left atrial map will be created (if needed).
  - Adjunctive assessment of anatomy and ablation sites with real-time electrogram monitoring, intracardiac echocardiography (ICE), and fluoroscopy will be performed as per standard.

## 10.4 POST-PROCEDURE

### 10.4.1 POST-PROCEDURE FOLLOW UP

- Discharge criteria decisions will be made at the discretion of the primary operator per current guidelines.
- Medication and adverse event review will be performed prior to discharge.
- Complications including vascular, stroke, heart failure, pericardial effusion, cardiac tamponade, bleeding, and death will be documented.

### 10.4.2 POST-PROCEDURE MEDICATION MANAGEMENT

- Standard cardiovascular medications are left up to the discretion of the investigator.
- Therapeutic anticoagulation beyond the requisite 2 months post-procedure time point will be at the discretion of the patient's physician.

## 11 SAFETY

We anticipate no significant increase in adverse events as compared to the standard AT/AF ablation procedures. The local site primary investigator will oversee the safety of the study at his/her site. As this is non-invasive mapping tool, we do not anticipate any adverse events unique to the case in itself. The operator may revert to using the standard non-study software at any point during the procedure at their sole discretion. The CT/MRI scan that is required is already part of the standard of care. A detailed tally of adverse events will be kept and they are defined as such.

**Adverse Events**

An adverse event is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an adverse event unless there is a change in the nature, severity or degree of the condition.

**Serious Adverse Event**

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

**Unanticipated Adverse Device Effects**

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

**Causality**

The investigator will assess the relationship of an adverse event to the intervention. Causality will be defined as follows:

*Probable*
Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the ablation procedure. The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the intervention, and
- The event is a known reaction to the intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

*Possible*
Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after intervention, and
- The event is not a known reaction to intervention, but cannot be explained by a commonly occurring alternative etiology

*Unlikely*
Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to intervention and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the intervention, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the intervention.

**Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects**

All investigators must report both expected (protocol-defined) and unexpected SAEs. All protocol defined SAEs must be reported directly to the clinical center's IRB and the DCC within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths, UADEs, and unexpected SAEs that are possibly or probably related to the mFAM guided procedure must be reported to the DCC and the clinical center's IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All unexpected SAEs that are unlikely related to the study intervention must be reported to the DCC and the clinical center's IRB within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

The DCC will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

**Reporting of Unanticipated Problems**

All UPs that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All UPs that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

**DCC Reporting to FDA**

The DCC will report unexpected SAEs that are possibly or probably related to the investigational device or UADEs to FDA as appropriate. The DCC will send an initial IDE safety report communication to the FDA within 2 business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of a UADE for this IDE trial.

**Data Monitoring Committee**

To meet the study's ethical responsibility to its subjects, an independent Data Monitoring Committee (DMC) will monitor results during the study. The DMC for this trial will consist of a single cardiologist who has no formal involvement or conflict of interest with the subjects, the investigators, the sponsor or the DCC. The DMC will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DMC will review interim summary results of the accumulating data every 6 months or as needed. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. The FDA will be provided a copy of any written communication from the DMC to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The DMC will be provided a copy of any letter from the FDA to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The clinical centers will have no contact with the DMC regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DMC members will not be allowed during DMC closed meetings. However, the PI will only be present at the open session of the meetings to clarify questions concerning the protocol and to provide updates to the DMC regarding pertinent new trial information. However, recommendations and decisions regarding the study are solely up to the discretion of the DMC.

## 12 RISKS

Patient confidentiality risks associated with any research study are minimal and include: breach of confidentiality and loss of personal data.

As the protocol includes a *standard of care* AF ablation procedure, *the risks of the procedure are generic to a standard AF ablation procedure, and include the following:*

Potential Risks Associated with AF Ablation

- Death: End of Life
- Stroke (also called Cardiovascular Accident or CVA): may cause an interruption in the blood supply to a part of the brain
- Pericarditis: inflammation may occur in the outer lining of the heart (<1%).
- Cardiac perforation causing pleural effusion or tamponade: fluid build-up around the heart. A hole in your heart wall (*perforation*) could result in bleeding into the sac, called the pericardium, which surrounds your heart (*cardiac tamponade*). This may be treated by insertion of a needle, through your chest wall, into the sac and removal of the blood. This type of hole sometimes requires surgical repair
- Heart Valve injury (also called Valvular Damage/Insufficiency): an injury to a valve structure resulting in a loss and/or worsening of function (e.g., worsening of regurgitation score or prolapse) (<1%).
- Acute Pulmonary edema: fluid accumulation (build-up) in the lungs (<1%).
- Pulmonary embolism: blockage of a pulmonary artery; a blood clot from a vein may get stuck in the lungs. This is usually treated with drugs (<1%).

- Vascular access complications: an obstruction or perforation or damage to the vascular (blood vessel) system (2%).
- Arterial/venous thrombus: clot formation in the artery or vein (1.5%).
- AV fistula: an abnormal passageway (such as a hole) between an artery and a vein; this may allow blood to go between the arteries and veins and not through the entire body. This may cause some part of the body to not receive the usual amount of blood. This may heal on its own, but may require surgical repair (1.5%).
- Catheter insertion site hematoma: bleeding or bruising from the site of catheter placement. This may go away without treatment, but may require manual compression or surgical repair. If excessive bleeding at the site of the catheter placement continues, this could result in anemia requiring medical intervention (2%).
- Hypoxia: reduced oxygen supply to tissue (<1%).
- Infection, Localized or systemic: an infection may occur anywhere an incision or cut is made during the procedure (<1%).
- Peripheral venous thrombosis: blood clots in the vein (<1%).
- Phrenic nerve damage: damage to the nerve that controls the diaphragm and may affect your breathing. Symptoms may be temporary but in some cases can be permanent (respiratory arrest) (<1%).
- Pneumonia: infection of lungs or gathering of fluid in the lungs (<1%).
- Pseudoaneurysm: development of a false pouch in the vessel wall. This can be caused by movement of catheters in the blood vessels. This may heal on its own, but sometimes need surgical repair (<1%).
- Radiation injury resulting in dermatitis (skin burns): (<1%).
- Respiratory failure: damage to breathing that can be permanent (respiratory arrest) (<1%).
- Radiation exposure during the fluoroscopic imaging of the catheters during ablation: this may slightly increase the lifetime risk of developing a fatal malignancy or a genetic defect in offspring (<1%).
- Fluid overload: excessive fluid built up could result in pulmonary (lung) edema; congestive heart failure (CHF) may occur or may be exacerbated (worsened) due to delivery of sterile salt water (saline) during the procedure (these risks are specific to open irrigated ablation catheters) (1.5%).

The protocol requires a CT or MRI scan be performed. Routine CT or MRI scanning with contrast is often performed if there are no contraindications as part of normal pre-procedural planning. If the patient has impaired renal functions or has abnormal renal function, CT/MR imaging will be deferred.

# 13 STUDY MANAGEMENT

## 13.1 STUDY DATA COLLECTION AND PROCESSING

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Patients will be identified by a 5-digit number and their initials. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers) for their own reference. All study-related documents (CRFs, source medical records, regulatory binder) must be kept in a secure, locked environment with access limited to study personnel only.

The PI is responsible for ensuring the following: 1) adherence to the protocol; 2) verifying adherence to local regulations on the conduct of clinical research; and 3) ensuring completeness, accuracy, and consistency of the data entered in the CRF.

Final CRFs in human readable format must be reviewed and verified for accuracy by the study site Principal Investigator and signed-off. A copy of the final CRF will remain at the investigator's site at the completion of the study.

The CRF numbering convention is as follows:

_01_-_2_ _3__4_ A -B -A
_01_: Site # must be 2 digits (use leading zero) --- (sites 01-2)

_2_ _3__4_: patient screening/enrollment # (001 – 050)—must be 3 digits

A-B-A: Patient initials (if no middle initial, use dash)

Total 5 digits and initials for enrolled patients.

### 13.2 CONFIDENTIALITY

Patient information will be kept confidential and managed according to the 1996 HIPAA guidelines. Each patient will be given a unique subject number and will be identified by this number and their initials. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is protected.

### 13.3 DEVIATIONS FROM PROTOCOL

The investigator will not deviate from the protocol except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the IRB/EC must be notified within five days of the incident.

### 13.4 ROLE OF THE COORDINATING CENTER

As principal investigator and study sponsor of this clinical study, Vivek Reddy, MD assumes the overall responsibility for the conduct of the study, including assurance that the study meets national and institutional guidelines for study conduct. In this study, Vivek Reddy, MD will have certain direct responsibilities and will delegate other responsibilities to his staff at the Coordinating Center, the Icahn School of Medicine at Mount Sinai. The coordinating center will: 1) ensure adherence to the national and institutional regulations; 2) develop and distribute protocols and case report forms; 3) coordinate data organization; 4) perform statistical analyses; 5.) provide on-site and remote monitoring.

### 13.5 WITHDRAWAL OF SUBJECTS

A subject may withdraw from the study at any time should they choose to do so. Additionally, subjects may be withdrawn by the investigator if deemed appropriate due to safety or compliance issues.

### 13.6 ECONOMIC IMPACT ON SUBJECTS

There are no additional costs related to involvement in this study. Since the cost of the procedure will be included within the Disease Related Group (DRG) charge, neither patient nor insurance provider will incur additional cost.

## 14 ETHICAL AND REGULATORY CONSIDERATIONS

### 14.1 MAINTAINING RECORDS (21 CFR 812. 140 (B))

All clinical sites will maintain study records for two years after research termination. The Coordinating center will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial.

### 14.2 INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC) INFORMATION

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by the IRB/EC before the change is made.

The study site Principal Investigator(s) is responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

## 15 CLINICAL CENTERS

The study will be conducted in up to 4 sites in the United States. Each clinical center will be required to obtain IRB/EC approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the DCC with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

**Investigator Profile**

All cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

**Qualifications and Training**

Clinical investigators will be electrophysiologists with expertise in AF ablation. The certified operator will either perform the ablation on their own patient, or participate in the ablation of an enrolled patient. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

## 16 DATA HANDLING

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

1. What protected health information (PHI) will be collected from patients.
2. Who will have access to that information and why.
3. Who will use or disclose that information.
4. The rights of a research patient to revoke their authorization for use of their PHI.

In order to ensure patient confidentiality, all case report forms and patient information (CT / MRI, if reviewed), fluoroscopic and endoscopic images, ECGs) will be de-identified and replaced with a unique patient identifier. Information will be stored in the office of the local study coordinator, which will be kept in a secure, locked location. The research study coordinators, principal investigator and co-investigators will be the only personnel with access to this data. All data will be stored without any patient information apart from the unique three digit patient identifier. Electronic data will be encrypted and password-protected.

## 17 DATA ANALYSIS

Baseline clinical characteristics (e.g. age, gender, renal function) and procedural characteristics (e.g. surface intracardiac electrogram, and imaging findings) of the patients will be collected and analyzed. All continuous variables will be performed as the mean ±standard deviation and all categorical variables as a percentage of the total study population.