# JHM IRB - eForm A – Protocol

## 1. Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with increasing morbidity and mortality. A catheter-based AF ablation technique that isolates pulmonary veins (PV) from the left atrium has been established to disrupt AF. Despite significant development, AF ablation with pulmonary vein isolation (PVI) is reported to have a success rate of 40-80% in various AF populations. Many factors noted in the occurrence and progression of AF namely genetic factors, clinical parameters including biomarkers, heart disease and extrinsic influences like sleep apnea, have also been noted to impose direct effect on its recurrence following an ablation procedure, whether PVI alone or with additional ablation lines. Although major developments in techniques and energy delivery systems have occurred since AF ablation was implemented a decade ago, little is known on the predictors of success or failure of the procedure.

Moreover, it is thought that a trigger-based mechanism is responsible for initiating AF. Several studies have localized these triggers to the PV antra. This has led to the development of a PV trigger ablation, or PVI, that proved to be particularly more successful in paroxysmal AF. In fact, persistent AF appears to be more reliant upon fibroblast proliferation and myocyte-fibroblast coupling than paroxysmal AF with obvious implications on its management. Despite our knowledge that fibrotic substrate is responsible for the perpetuation of persistent AF, several ablation techniques targeting these extra-pulmonary veins sites have failed to prove an additional benefit to PVI alone. Nevertheless, two recently developed technologies, aimed at detecting AF substrate with high precision, seem to constitute a potential breakthrough in the management of persistent AF. On one hand, late gadolinium-enhanced MRI (LGE-MRI) is a well-established method to identify fibrosis in the myocardium. Recent reports from a single center have shown that MRI-based left atrial fibrosis detection is able to predict the outcome of the procedure. Hence, targeting lesions seen on LGE-MRI in the setting of persistent AF is an option yet to be explored and compared to the widely adopted, yet suboptimal, PVI. On another hand, a novel ablation method with promising results is focal impulse and rotor modulation (FIRM). Undergoing wide sampling of the atria with spatiotemporal and computational mapping while in AF has identified areas with stable organized rotational electrical activity (rotors). Several studies are under way to prove the reproducibility of rotor mapping, with more groups reporting improved rates of acute and long-term suppression of AF with ablation of FIRM-identified rotors. (Narayan et al., 2014; Shivkumar, Ellenbogen, Hummel, Miller, & Steinberg, 2012) (Akoum et al., 2015)

The SIMPle AF study will be a randomized clinical trial designed to test the hypothesis that ablation tailored to the underlying substrate using either LGE-detected dense scar or rotor anchor sites predicted by computational modeling is superior to anatomic non-tailored PVI ablation in patients with persistent AF. For the present study, we plan to enroll a total of 30 patients. Following the collection of preliminary outcome data, we plan on enlarging the study to a multicenter randomized controlled trial enrolling a total of 300 patients, with the support of an NIH grant.

## 2. Objectives

The main objective of the study is to identify the optimal ablation strategy for suppression of persistent AF.

The secondary objectives of the study are:

- To define the local myocardial image characteristics of slow conduction AF substrates.
- To define the local myocardial structural changes post ablation that associate with AF suppression at 1-year follow-up
- To compare cardiac remodeling and atrial function at 1-year follow-up between PVI only and tailored catheter ablation groups

## 3. Background

Atrial fibrillation (AF) is associated with increased risk for mortality, heart failure, and thromboembolic events, and has a worldwide prevalence of >33.5 million (Benjamin et al., 1998; Chugh et al., 2014; Estes et al., 2011; Schnabel et al., 2015). Catheter ablation of AF is evolving as an effective therapy for symptomatic AF (Calkins et al., 2012). Recurrent AF after ablation, however, remains a problem and has been reported to associate with the baseline extent of left atrial (LA) late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) (Marrouche et al., 2014; McGann et al., 2014). Mechanistically, persistent AF appears to be more reliant upon fibroblast proliferation and myocyte-fibroblast coupling than paroxysmal AF, which is primarily dependent upon pulmonary vein triggers (Haissaguerre et al., 1998; Inoue et al., 2012; Wilber, 2012). Therefore, we hypothesize that the substrate for persistent AF is detectable on atrial LGE-CMR and variable among patients, and that the substrate predicts patient outcomes after anatomic non-tailored ablation, and is more likely to respond to individually tailored ablation approaches. Two individually tailored approaches will be studied including empiric targeting of dense LGE, confirmed on bipolar mapping to have voltage <0.1 mV, and modeling based targeting of rotor anchor sites.

## 4. Study Procedures

a. Study Design

Initially, we propose prospective enrollment of 30 participants with persistent AF. Patients presenting to our institution who meet the inclusion criteria will be asked to participate in the study. All patients will undergo routine clinical care including echocardiography as indicated.

All patients will undergo a LGE-MRI within 30 days prior to the ablation procedure. The clinical purpose of the initial MRI is to define the anatomy of the heart chambers as well as the vessels for procedure planning. For research purposes, we will use this initial clinical MRI to delineate atrial structural remodeling or fibrosis to be used during the procedure in patients randomized to group 2 (pulmonary vein isolation + scar-based ablation) and for later analysis in all patients.

Imaging is done at our institution and will be reviewed for quality by the study staff. LGE-MRI sequences that do not meet quality standards for fibrosis analysis will not be further processed and these patients will be excluded from the study. Subjects for whom images are successfully evaluated will be randomized to the study groups.

This will be followed by block randomization in 1:1:1 format to a) pulmonary vein isolation (PVI) only (current standard of care), b) PVI plus targeting of dense LGE sites, which are confirmed on bipolar mapping to have voltage <0.1 mV, and c) PVI plus targeting of rotor anchor sites predicted by modeling.

At baseline, all patients will be evaluated for their quality of life (QOL) using the Short-form health survey (SF-36) (Ware & Sherbourne, 1992) for overall as well as AF-related impact on quality of life (Refer to additional study documents). The severity of symptoms will be tested using the European Heart Rhythm Association (EHRA) score of atrial fibrillation and the Canadian Cardiovascular Society (the CCS-SAF) scale (Dorian et al., 2006). Clinical data will be stored electronically and linked to a specific research ID number. Information linking de-identified data to the patients will be stored in the locked research office, in a password-protected file. Only members of the research team, in charge of collecting clinical information, will have access to this file. Individual subject binders containing signed consent forms and clinical source documentation will be labeled using study subject numbers and stored in the locked research office mentioned previously.

A pre-ablation cardiac MRI is clinically indicated to assess baseline cardiac anatomy prior to procedure. Routine and LGE protocols will be used to acquire MR images. All patients will be asked to undergo a repeat LGE-MRI 12 months after the ablation. This is done for research purposes. Renal function is routinely monitored prior to gadolinium-enhanced MRI as a standard of clinical care.

With regards to the ablation procedure, all patients will undergo AF ablation. The procedure consists of circumferential pulmonary vein lesions under electro-anatomical guidance using CARTO (Biosense Webster Inc., Diamond Bar, CA). Operators will use either a 3.5mm irrigated tip radiofrequency ablation catheter (ThermoCool SmartTouch, Biosense Webster Inc., Diamond Bar, CA) or a cryoballoon catheter (Arctic Front Advance, Medtronic Inc., Minneapolis, MN). This procedure is FDA approved and will be conducted in all treatment arms according to standard of care. However, patients in the second group will undergo additional targeting of dense LGE sites, confirmed on bipolar mapping to have voltage <0.1 mV and patients in the third group will undergo targeting of rotor anchor sites as predicted by computational modeling. A detailed protocol of rotor ablation is described in the literature and shows no added complications compared to the conventional procedure (Narayan et al., 2014).

To prevent short-term recurrence of AF, patients will be kept on anti-arrhythmic regimen for the first 1 to 3 months after the ablation to be discontinued thereafter in the absence of AF recurrence, at the discretion of the treating physician. In addition, standard protocols for anticoagulation prior to, during, and after the ablation procedure will be applied.

After the ablation, clinical follow-up visits are scheduled at 3, 6 and 12 months. Research follow-up questionnaires and 12-lead ECG recordings will be done at the same day of the visits. All patients will undergo rhythm monitoring to detect AF recurrence using a portable, smartphone operated, AliveCor® Mobile ECG device. The AliveCor® Mobile ECG is a mobile, clinical-quality electrocardiogram (ECG) recorder. The software application can store thousands of recordings on smartphones or tablets and these recordings are wirelessly transmitted to AliveCor, Inc. (AliveCor) servers accessible to authorized users including healthcare providers. This device will be provided to the patients at no cost after enrollment in the study.

Prior to ablation, patients will be asked to complete 7 days of twice-daily 1-minute rhythm monitoring using the AliveCor® device. After the procedure, follow-up will be done on a weekly basis through trans-telephonic transmissions of ECG recordings. Periodic reminders will be sent to patients (via telephone, email, or mail) regarding follow up transmissions in the event that a weekly transmission is missed. Although preferred, it is not imperative that all patients complete all weekly follow up transmissions.In addition, study participants will be advised to provide recordings if they experience heart-related symptoms (palpitations, shortness of breath, rapid heartbeat, chest pain). This extensive rhythm monitoring protocol is not standard of care and is done for research purposes. Review of the rhythm monitoring data will be performed in accordance with current clinical guidelines. The device software and the investigators will analyze rhythm strips and a report will be available to the research team and to the treating physician upon his/her request.

In addition, upon detection of any arrhythmia with important clinical implications, the investigators will notify the electrophysiologist involved in the care of the patient. The research team may contact the patient directly if prompt action is advised, such as reporting to the local emergency room or following up with their electrophysiologist. The rhythm monitoring protocol utilized in this study may result in unscheduled visits to the physician. If a repeat ablation procedure is indicated, it will be scheduled according to standards of clinical care.

A detailed study timeline is attached at the end of the document.

b. Study duration and visits.

We aim to complete the proposed study protocol in two years. After the ablation, patients will be followed at 3, 6 and 12 months via in clinic visit; a 1 month and 9 month follow up will take place via remote ECG transmission. Follow-up research questionnaires and post-ablation MRI will be scheduled to coincide with the routine clinical visits. Hence, no additional visits will be required of research participants unless it was not possible to schedule the MRI on the same day as clinic visits. Only then will we ask participants to present to JHH for the follow-up MRI.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
N/A

d. Justification of why participants will not receive routine care or will have current therapy stopped.
N/A

e. Justification for inclusion of a placebo or non-treatment group.
N/A

f. Definition of treatment failure or participant removal criteria.
N/A

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
N/A

## 5. Inclusion/Exclusion Criteria

a. Inclusion Criteria

Patients are eligible for the SIMPle AF study if they are 18-100 years of age, have a history of persistent atrial fibrillation, are indicated for an AF ablation procedure, and agree to participate in the SIMPle AF trial.

b. Exclusion Criteria

- Are unable or unwilling to provide informed consent for the SIMPle AF study
- Patients with cardiac devices like pacemakers, internal cardiac defibrillators and Cardiac Resynchronization Therapy Device (CRT)**.** Patients with acute or chronic renal insufficiency (glomerular filtration rate <30 ml/min/1.73 $m^2$), or patients in the perioperative liver transplantation period
- Pregnant women
- Patients who are unable to adhere to the follow up protocol

- Patients with contraindication to MRI, including ferromagnetic aneurysm clips, metal in the eye, and implanted ferromagnetic or other MRI-incompatible devices
- Patients in whom the LGE Cardiac MRI does not meet quality standards for fibrosis analysis
- Subjects without daily access to a smart phone or tablet compatible with the AliveECG application and ability to upload ECG tracings for the follow up period
- Patients with a history of allergic reactions to gadolinium-based contrast agents or ingredients and will not be premedicated**

****Subjects with a history of reaction to contrast may be premedicated according to institutional protocol prior to receiving intravenous contrast agents**

## 6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Patients undergoing MRI angiogram are routinely injected with gadolinium as contrast. Gadolinium-based MRI contrast agents are used to visualize scar/ablation lesions in the atrial wall (McGann et al., 2014). Gadolinium chelates used as intravenous contrast media are extremely safe in patients with normal kidney function and do not exhibit the nephrotoxicity associated with iodinated media. Minor reactions including nausea and hives may occur in a small percentage of cases. Severe anaphylactic reactions are extremely uncommon (Runge, 2001).

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Gadolinium (total dose of 0.2 mmol/kg) will be administered 10 minutes prior to delayed enhancement imaging to evaluate for the presence of myocardial scar. Gadolinium-based contrast agents are not FDA-approved for diagnosis of cardiac disease by MRI. However, these agents have been routinely used for more than 10 years at the JHH and other centers for clinical and research purposes to evaluate diseases of the myocardium and vessels (Akoum & Marrouche, 2014) (Zareian et al., 2015). The standard gadolinium dose at JHH and other institutions in cardiac MRIs is a maximum of 0.2 mmol/kg.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. N/A

## 7. Study Statistics

a. Primary outcome variable.

Data from AliveCor® Mobile ECG rhythm device recordings, follow-up visits (examinations and ECGs), and QOL/follow-up questionnaires will be used to identify the success rates of the procedure. Procedure failure is defined as symptomatic or asymptomatic AF/Atrial flutter/Atrial tachycardia of at least 30 seconds duration that is documented by an ECG or device recording system, occurring after the 3-month blanking period following catheter ablation. Individually tailored ablation strategies for suppression of persistent AF have not been investigated. We hypothesize that individually tailored ablation strategies will improve AF/AT suppression compared to PVI alone. The association of time to AF/AT recurrence with ablation strategy will be examined in 30 randomized patients.

b. Secondary outcome variables.

During ablation, the spatial coordinates and electrogram characteristics of >200 intra-cardiac points are sequentially sampled and saved. We hypothesize that sites with slow conduction during sinus rhythm,

representing AF substrates, are detectable as sectors with intermediate LGE intensity [image intensity ratio (IIR) 0.9-1.6] on LGE-CMR. We will co-register the spatial coordinates of sites exhibiting slow conduction with pre-procedural LGE-CMR for 30 patients. We will then compare the baseline image intensity ratio of sites with slow conduction versus other sites.

Catheter ablation results in long-term AF suppression in approximately 50% of patients with persistent AF. We hypothesize that AF suppression at 1-year will be associated with the presence of IIR>1.6 at the 1-year LGE-CMR in sectors where slow conduction was observed at baseline. We will co-register the baseline spatial coordinates of sites exhibiting slow conduction with 1-year post-procedural LGE-CMR images for 30 patients randomized to ablation. We will then compare the 1-year image characteristics of sectors with slow conduction among patients with and without AF suppression at 1-year follow-up.

Catheter ablation promotes scar formation and more extensive ablation strategies may adversely affect left atrial function. However, AF recurrences and continuation of antiarrhythmic drug therapy may also lead to progression of atrial and ventricular dysfunction. We hypothesize that more extensive patient tailored approaches will have less negative impact on atrial and overall cardiac function. We will measure the change (baseline to 1-year MRI) in left atrial and left ventricular regional and global strain in 30 randomized patients. We will then examine the association of the change in regional and global strain with ablation strategy.

c. Statistical plan including sample size justification and interim data analysis.

Based on the variable success rate of 40-80% in AF ablation, we anticipate that the study cohort of 30 patients would produce adequate sample size in all treatment arms and be sufficient to make meaningful statistical comparison.

Comparison variables will be presented as means ± SD, and categorical variables as numbers and percentages. Differences between treatment groups will be assessed using the Pearson Chi-square test and the Wilcoxon rank-sum test. Survival curves for time to event analysis will be estimated using the Kaplan-Meier method, and the differences between the curves will be tested for significance with the log-rank statistic. Weekly event rates will be calculated by dividing the event rate by the maximum follow-up period in each arm of the Kaplan-Meier analysis. Hazard ratios will be calculated by univariate and multivariate analysis using the Cox proportional-hazards regression model. When comparing MR image characteristics as well as LA function between pre and post-ablation imaging, the Student's t-test will be using for comparison of the means. All statistical testing will be 2-tailed. Results will be considered statistically significant at a level of $p<0.05$.

d. Early stopping rules. N/A

## 8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

As discussed above, all procedures except the post-ablation MRI is part of the standard clinical care. In addition, groups reporting their experience with substrate-based ablation have not encountered increased complications compared to the conventional ablation procedure (Narayan et al., 2012). In addition, there is no data suggesting any health hazard associated with magnetic field exposure (Schenck, 2000). All patients with pacemakers, implanted defibrillators or electronic/metallic devices, shrapnel and other metals such as metal in the eyes will be excluded.

Gadolinium chelates used as intravenous contrast media in MRI are considered safe and do not exhibit the nephrotoxicity associated with iodinated media. The injection of contrast intravenously is not painful, but

may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% of people and are short-lived. Allergic reactions to contrast are extremely rare and the risk of a severe reaction is less than 1 in 300,000. Recently, gadolinium-based contrast has been reported to cause Nephrogenic Systemic Fibrosis (NSF) in patients on dialysis or renal failure. The FDA has issued warnings with regards to this issue ((FDA), 2010). Hence, patients with renal failure and those on dialysis will be excluded from our study.

b. Steps taken to minimize the risks.

Patients will be monitored for acute symptoms of hypersensitivity after contrast administration including hives, flushing, and nausea. Patients with acute or chronic renal insufficiency (GFR <30ml/min/1.73m$^2$), or patients in the perioperative liver transplantation period are at risk of developing NSF. To minimize the risks, such patients will be excluded from the study.

All standard pre-procedure activities i.e. pregnancy testing and renal function testing will be conducted by JHH staff according to standard institutional protocol.

c. Plan for reporting unanticipated problems or study deviations.

The study team will maintain reporting in accordance with the JH IRB's AE and SAE reporting criteria.

d. Legal risks such as the risks that would be associated with breach of confidentiality. N/A

e. Financial risks to the participants.

All MRIs performed post-ablation will be provided at no cost if not indicated clinically. The AliveCor® Mobile ECG devices will also be provided at no cost. All other tests and follow-up visits are part of routine clinical care and will be billed to insurance.

## 9. Benefits

a. Description of the probable benefits for the participant and for society.

Patients enrolling in this study may not experience direct benefit from this study. However, the results of the study may benefit those with atrial fibrillation. The SIMPLE-AF study aims to improve the efficacy, safety and outcomes of the ablation procedure for persistent AF. By improving the rate of AF recurrence, we will also reduce the overall economic burden of AF. Potential long-term side effects of the procedures at hand will be investigated, as well as ways to avoid it.

## 10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There is no compensation or penalty related to the decision to participate in the study.

## 11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The pre-ablation MRI is standard of care for any patient undergoing atrial fibrillation ablation and will therefore be billed to insurance.

The rhythm monitoring devices will be provided to the participants at no cost.

As mentioned in section 1, we plan to apply for a grant from the NIH (NHLBI) in order to expand the SIMPle AF study to a multicenter trial with a sample size of 300 patients following the collection of preliminary outcome data on roughly 30 subjects. This will provide a unique opportunity to investigate disease progression and the mechanism of action of our interventions in the context of persistent AF.

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# APPENDIX

## A. STUDY PROTOCOL TIMETABLE

| | Screening/ Pre-Ablation | Ablation | 1-Month Follow-up | 3-Month Follow-up | 6-Month Follow-up | 9-Month Follow-up | 12-Month Follow-Up |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| History and Physical Exam | X | | | X | X | | X |
| 12-Lead ECG | X | | | X | X | | X |
| Echocardiography | X (As indicated) | | | | | | |
| AliveCor® Rhythm Monitoring | X | | X | X | X | X | X |
| LGE-MRI | X | | | | | | X |
| Follow-up Questionnaire | X | | | X | X | | X |