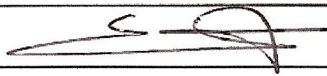
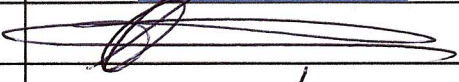


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**SUBSTRATE AND TRIGGER ABLATION FOR  
REDUCTION  
OF ATRIAL FIBRILLATION TRIAL – PART II  
**STAR AF II**  
AF-09-102-ID-AB  
Clinical Investigational Plan (CIP)**

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## **2 BACKGROUND**

Atrial fibrillation (AF) is a very common arrhythmia affecting 1-2% of the American and Canadian population<sup>1</sup>. AF significantly impairs quality of life, increases the risk of stroke, and is associated with increased overall mortality<sup>2-5</sup>. Treatments to effectively eliminate AF and maintain sinus rhythm may not only improve patient quality of life, but may even reduce mortality<sup>6</sup>.

Recently, percutaneous catheter ablation has emerged as an effective, curative treatment for AF<sup>7-9</sup>. Initial techniques of ablation were developed based on the observation that AF was often triggered by frequent ectopic atrial activity emerging from the pulmonary veins<sup>7</sup>. By ablating these ectopic foci, AF initiation could be prevented in a substantial number of patients with paroxysmal AF<sup>7</sup>. In order to avoid the potential complication of pulmonary vein (PV) stenosis, and to improve success rates, the procedure has evolved<sup>10</sup>. While early procedures isolated the PVs at the level of the ostium, present-day procedures isolate outside of the tubular portion of the veins at the level of the funnel-shaped venous-atrial interface, sometimes referred to as the PV antrum (PVA)<sup>8,11,12</sup>. By isolating the PVAs from the atrium, ectopic activity from the PVs are no longer able to trigger AF. Single center experiences, and limited randomized trial data, have suggested reasonable success rates of PVA isolation for paroxysmal AF, ranging from 60-90% after one or two procedures<sup>9,11,12</sup>. In fact, the 2007 Heart Rhythm Society Consensus Statement on Catheter Ablation of AF states that PV isolation has become the “cornerstone” of present-day AF ablation<sup>22</sup>.

However, data on the efficacy of this so-called “trigger-based” strategy for more persistent AF populations is conflicting. First of all, the definition of “persistent” AF differs in the published literature, encompassing patients who have longer paroxysms of AF that are cardioverted early to patients who have permanent AF for years. Thus, the persistent AF population is not homogeneous and it should therefore not be surprising that success rates of a procedure would vary. Many reports have described reasonable success rates for PV isolation in mixed paroxysmal and persistent AF populations, but it is difficult to assess the success rates for each population separately from these studies. Others have suggested that PV isolation may achieve success rates in persistent AF comparable to paroxysmal AF after one or two procedures. More recent data, however, suggests that PV isolation achieves only moderate success in persistent AF, and that the success rates may be 15-40% lower than those quoted for paroxysmal AF<sup>14</sup>. Furthermore, the incidence of repeat ablation procedures with PV isolation alone may be higher in persistent AF. Thus, while trigger-based ablation is the most common technique for AF ablation, it may or may not be adequate for targeting higher burden AF populations.

In patients with persistent AF, it is believed that there may be additive benefit to targeting the atrial substrate responsible for AF maintenance in addition to the triggers for AF initiation. However, the best method to characterize and target this so-called “substrate” remains somewhat elusive. Creation of linear lesions across critical structures of the left and/or right atrium has been used for this purpose. From the early surgical experiences with the Maze and modified Maze procedures, creation of

complete linear lesions may be very effective in preventing the development of AF. One mechanism by which this may work is division of the atrium into isolated segments that are too small to sustain the multiple wavelets required to perpetuate AF. Another mechanism may be that linear lesions prevent development of macro-reentrant atrial flutters/tachycardias which are a frequent cause of recurrence post-catheter ablation of AF. Finally, linear lesions may transect structures that harbor key rotors for AF maintenance, such as the posterior wall, the PV antral border, the roof, and the septum. Single-center studies have suggested that addition of linear lesions to PV isolation may improve procedural efficacy for both paroxysmal and persistent AF. Others have suggested that addition of linear lesions is essential for prevention of iatrogenic flutters/tachycardias. Another study showed that addition of linear lesions may have equivalent or better efficacy to ablation of other adjuvant targets such as complex fractionated electrograms. The data is not all consistent, however, with some data showing that linear ablation may not add much to PV isolation. Furthermore, creation of linear lesions with documentation of conduction block can be time-consuming and hard to demonstrate, particularly along the mitral annulus and the septum. Creation of linear lesions without complete block may also be proarrhythmic.

Complex fractionated electrograms (CFE) may represent another target for the substrate for AF maintenance. CFE are very rapid or continuously fractionated electrograms that may represent key “rotor” or “pivot points” where wavelets can turn around and create opportunities for reentry that maintain AF<sup>15,16,17</sup>. One study suggested that targeting CFE alone, without PV isolation, can eliminate AF with high success rates in excess of 70%<sup>24</sup>. However, this result has not been duplicated by other investigators. Instead, CFE may be a useful adjuvant target to PV isolation, increasing success rates over trigger-based ablation alone. In the pilot STAR-AF trial (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation)<sup>23</sup>, we found that CFE alone was not an effective approach for AF ablation in high-burden paroxysmal and persistent patients. However, when CFE was combined with PV isolation, the strategy was more effective than either approach alone, with some suggestion of greater effectiveness in those with persistent AF. The patient numbers for this subgroup analysis were quite small, however, so the data was not conclusive. Furthermore, while some studies have supported the addition of CFE ablation for persistent AF, others have not. One of the greatest problems is in the subjectivity in identifying CFE. With the use of automated CFE mapping algorithms, localization of CFE may be more objective and consistent, with better results compared to visual identification alone. CFE regions may also demonstrate greater temporal and spatial stability when electrograms are analyzed over a short period of time, as happens with automated algorithms.

Data from a monocenter study suggested the combination of PV isolation with linear ablation and targeting of CFE<sup>25</sup>. While this procedure may reach the highest success rates, it is a very time-consuming process. Often, these procedures are over 6-8 hours in duration and often require two or more visits to the electrophysiology lab. Furthermore, many of the patients in the report remained on antiarrhythmic medications, so it is unclear what the additive benefit of such an extensive procedure is in comparison to linear or CFE adjuvant ablation alone.

To date, there is no randomized, multicenter trial addressing the best approach to AF ablation in persistent AF. However, this particular group of patients represents the

fastest rising group being ablated in most centers, and the majority of AF patients in the population. It is unclear if PV antral isolation (PVI) is sufficient as a lone strategy for persistent AF. Furthermore, if additional substrate ablation is to be added, it is unclear if linear (PVI+Lines) or CFE ablation (PVI+CFE) should be the approach of first choice. Thus, there is a good rationale for determining the best approach to AF ablation – trigger or combined trigger and substrate – in patients with persistent AF.

### **3 OBJECTIVES**

#### **3.1 PRIMARY OBJECTIVES**

- 3.1.1 The primary objective of this investigation is to compare the efficacy of three different AF ablation strategies in patients with persistent AF targeting:
- 3.1.1.1 Only the triggers of AF via PV antrum isolation (PVI) alone;
  - 3.1.1.2 A combination of the triggers plus the substrate of AF as defined by complex fractionated electrograms (PVI+CFE); and
  - 3.1.1.3 A combination of the triggers plus the substrate of AF by empiric linear ablation (PVI+Lines).

#### **3.2 SECONDARY OBJECTIVES**

- 3.2.1 The secondary objectives of this investigation are to evaluate and compare:
- 3.2.1.1 The safety and procedural characteristics of:
    - PVI alone versus
    - PVI+CFE versus
    - PVI+Lines.
  - 3.2.1.2 The quality of life between patients treated with:
    - PVI alone versus
    - PVI+CFE versus
    - PVI+Lines.

## **4 ENDPOINTS**

### **4.1 PRIMARY ENDPOINT**

- 4.1.1 Freedom from documented AF episodes > 30 seconds at 18 months after one or two ablation procedure with/without antiarrhythmic medications.

### **4.2 SECONDARY ENDPOINTS**

- 4.2.1 The secondary endpoints of this investigation are:
  - 4.2.1.1 Freedom from documented atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 4.2.1.2 Freedom from documented atrial flutter and atrial tachycardia episodes > 30 seconds at 18 months after one and two procedures with/without antiarrhythmic medications;
  - 4.2.1.3 Freedom from any atrial arrhythmia (documented or not) episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 4.2.1.4 Freedom from symptomatic AF episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 4.2.1.5 Freedom from symptomatic atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 4.2.1.6 Incidence of peri-procedural complications, including stroke, PV stenosis, cardiac perforation, esophageal injury and death.
  - 4.2.1.7 Procedure duration;
  - 4.2.1.8 Fluoroscopy time;
  - 4.2.1.9 Number of repeat procedures;
  - 4.2.1.10 Effect of each strategy on AF cycle length/regularity/termination;
  - 4.2.1.11 Relationship of acute termination of AF to long-term procedural outcome;
  - 4.2.1.12 Percentage achievement of complete linear block in linear ablation arm;
  - 4.2.1.13 Effect of complete linear block on procedural outcome in linear ablation arm;
  - 4.2.1.14 Quality of life measurements (SF-36, EQ-5D and CCS SAF) at baseline, 6, 12 and 18 months after one and/or two ablation procedures;
  - 4.2.1.15 Correlation of AF burden to symptoms and quality of life changes;
  - 4.2.1.16 Improvement in AF burden by > 90% post ablation procedure;



- 4.2.1.17 Relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome;
- 4.2.1.18 Cut off of AF burden that affects the Quality of Life measurement; and
- 4.2.1.19 Evaluation of cost effectiveness.

## **5 PATIENT SELECTION CRITERIA**

### **5.1 PATIENTS ENROLLMENT**

A patient who meets all the inclusion criteria and does not meet any of the exclusion criteria is eligible to participate in the investigation. A patient is enrolled in the investigation only when s/he has provided written informed consent. Once enrolled, a patient is expected to comply with the scheduled visits and required activities according to the protocol.

### **5.2 INCLUSION CRITERIA**

- 5.2.1 Patients age is 18 years or greater;
- 5.2.2 Patients undergoing a first-time ablation procedure for AF;
- 5.2.3 Patients with persistent AF;
  - 5.2.3.1 Persistent AF will be defined as a sustained episode lasting > 7 days and less than 3 years.
- 5.2.4 Patients with symptomatic AF that is refractory to at least one antiarrhythmic medication;
  - 5.2.4.1 Symptomatic patients are those who have been aware of their AF at anytime within the last 5 years prior to enrollment. Symptoms may include, but are not restricted to, palpitations, shortness of breath, chest pain, fatigue, left ventricular dysfunction, or other symptoms, or any combination of the above.
- 5.2.5 At least one episode of persistent AF must have been documented by ECG, holter, loop recorder, telemetry, trans telephonic monitoring (TTM), or implantable device within last 2 years of enrollment in this investigation;
- 5.2.6 Patients must be able and willing to provide written informed consent to participate in this investigation; and
- 5.2.7 Patients must be willing and able to comply with all peri-ablation and follow-up requirements.

## 5.3 EXCLUSION CRITERIA

- 5.3.1 Patients with paroxysmal AF;
  - 5.3.1.1 Paroxysmal AF will be defined as a sustained episode lasting < 7 days.
- 5.3.2 Patients with long-standing persistent AF;
  - 5.3.2.1 Long-standing persistent AF will be defined as a sustained episode lasting more than 3 years.
- 5.3.3 Patients for whom cardioversion or sinus rhythm will never be attempted/pursued;
- 5.3.4 Patients with AF felt to be secondary to an obvious reversible cause;
- 5.3.5 Patients with contraindications to systemic anticoagulation with heparin or coumadin or a direct thrombin inhibitor;
- 5.3.6 Patients with left atrial size  $\geq 60$  mm (2D echocardiography, parasternal long axis view); and
- 5.3.7 Patients who are pregnant.
  - 5.3.7.1 Pregnancy will be assessed by patients informing the physicians.

## **6 INVESTIGATION DESIGN**

### **6.1 TYPE**

- 6.1.1 This investigation is a randomized, prospective, parallel, single-blind multicenter design.

### **6.2 DURATION**

- 6.2.1 The first enrollment is anticipated in Q3 2010.
- 6.2.2 The enrollment period will be approximately 18 months.
- 6.2.3 The patient will participate in this investigation for approximately 18 months from enrollment to the last follow-up.
- 6.2.4 The patient may withdraw from the investigation at any time, for any reason. In this case, the procedures for reporting should be followed as mentioned in the section 9.4 Early Conclusion to Patient Participation.

### **6.3 ENROLLMENT TARGET**

- 6.3.1 The enrollment target for this investigation is 549 patients. For more information, refer to section 8.1 Sample Size Justification.

### **6.4 RANDOMIZATION**

#### 6.4.1 Randomization Stratifications

- 6.4.1.1 Randomization is stratified by center.

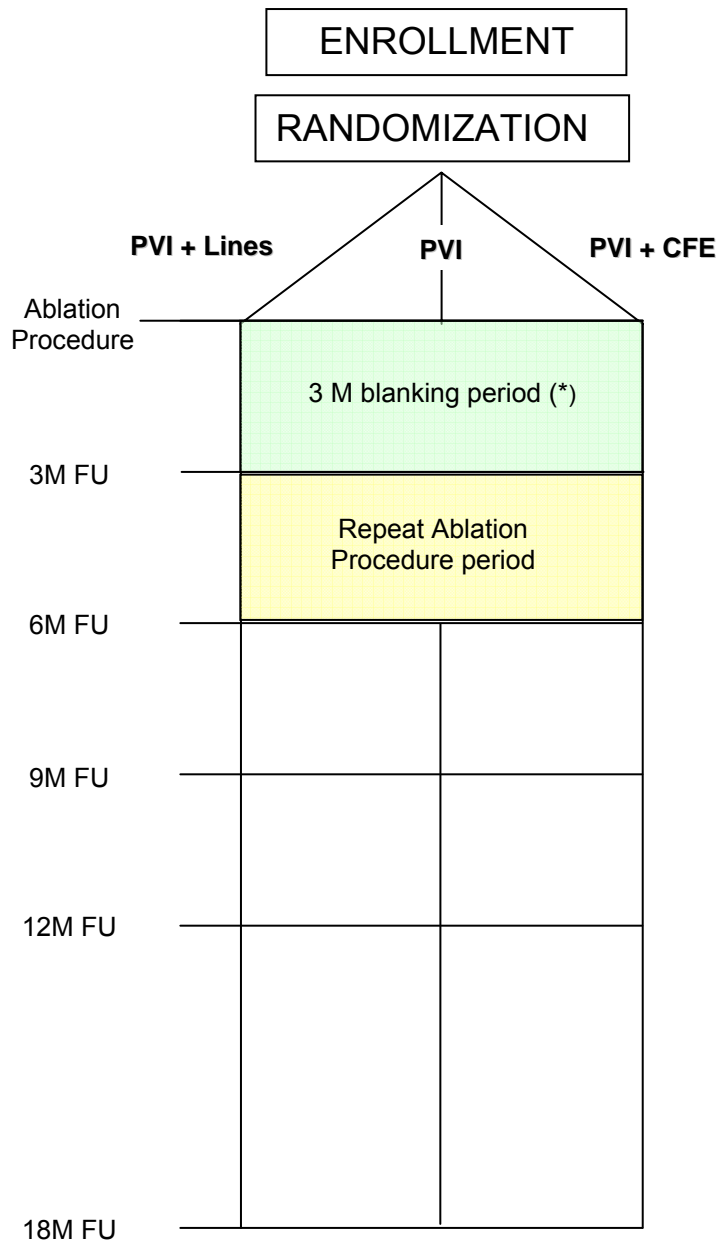
#### 6.4.2 Randomization Arms

- 6.4.2.1 Patients are randomized in a 1:4:4 fashion to one of the investigation arms:

- Pulmonary vein antrum isolation alone (**PVI**);
- Pulmonary vein antrum isolation plus ablation of complex fractionated electrograms (**PVI+CFE**);
- PVI plus empiric linear ablation (**PVI+Lines**).

6.4.2.2 Because of the nature of the ablation procedures, physicians cannot be blinded to the randomization. Patients will be blinded to their ablation strategy (single-blind design).

## 6.5 DESIGN



(\*) AF/AT/AFL recurrence during the blanking period will not be taken into account.

## **7 PRODUCT**

### **7.1 PRODUCTS**

The following market approved St. Jude Medical products are required to be used in the investigation:

- 7.1.1 Cardiac Mapping System - Ensite NavX System; and
- 7.1.2 EnSite Complex Fractionated Electrograms Algorithm – CFE.

NOTE: The protocol will be opened to any new commercially available products.

### **7.2 ADDITIONAL PRODUCTS**

The following market approved products are required to be used in the investigation regardless of the manufacturer:

- 7.2.1 Open irrigated tip ablation catheter;
- 7.2.2 Radiofrequency (RF) ablation system;
- 7.2.3 Coronary sinus electrophysiology catheter (minimum 4 electrodes); and
- 7.2.4 Circular mapping catheter (minimum 10 electrodes).

The following market approved products are recommended to be used in the investigation regardless of the manufacturer:

- 7.2.5 Steerable and fixed introducers.

## 8 SCIENTIFIC SOUNDNESS

### 8.1 SAMPLE SIZE JUSTIFICATION

- 8.1.1 The sample size calculation is based on the hypothesis and study design. It is expected that the survival proportion (Freedom from AF) in PVI+CFE group is 75%, the survival proportion (Freedom from AF) in PVI+Lines group is 60% and the survival proportion (Freedom from AF) in PVI group is 45%. A one-sided log rank test was used for sample size calculation.
- 8.1.2 In order to test if the PVI+CFE strategy is superior to the PVI+Lines strategy and PVI strategy, a total of 468 patients is needed to maintain a overall power of 90% at a significance level of 5%, and with randomization ratio of 1:4:4 (PVI: PVI+CFE: PVI+Lines), 52 patients in PVI group, 208 each in PVI+CFE group and PVI+Lines group are needed.
- 8.1.3 Taking into account the drop out of 15%, a total of 549 patients (61 in PVI group, 244 each in PVI+CFE group and PVI+Lines group) will be recruited.

### 8.2 HYPOTHESES

- 8.2.1 The combined trigger and substrate approaches (PVI+CFE) will be superior to the triggers and linear ablation approach (PVI + Lines) and trigger-based strategy alone (PVI) in terms of freedom from AF at 18 months after one or two ablation procedure.

$$8.2.1.1 \quad H_0 : S_{COM} \leq S_{Line} \quad vs \quad H_1 : S_{COM} > S_{Line}$$

$$8.2.1.2 \quad H_0 : S_{COM} \leq S_{PVI} \quad vs \quad H_1 : S_{COM} > S_{PVI}$$

- 8.2.2 Where  $S_{COM}$  is the survival proportion (Freedom from AF) at 18 month after one or two ablations in PVI+CFE group;  $S_{Line}$  is the survival proportion (Freedom from AF) at 18 month after one or two ablations in PVI+Lines group;  $S_{PVI}$  is the survival proportion (Freedom from AF) at 18 month after one or two ablations in PVI group.

### **8.3 PRIMARY ENDPOINT ANALYSIS**

- 8.3.1 The primary endpoint analyses will be based on the intention-to-treat (ITT) principle comparing treatment randomized and all protocol deviators will be included. Secondary per-protocol (PP) analyses will compare patient data based on the actual treatment received and will exclude protocol deviators.
- 8.3.2 The log rank test will be used for the hypothesis and a p value of less than 0.05 will be considered to indicate statistical significance. Besides, the length of time to the recurrence of AF in each group was compared visually by the Kaplan–Meier curves.
- 8.3.3 Any baseline demographic factor, which is found to be significantly different between the treatments, will be assessed its impact on the primary endpoint analysis. For this purpose, a Cox regression model with treatment and above baseline factor will be used.

### **8.4 SECONDARY ENDPOINT ANALYSIS**

- 8.4.1 All time to event endpoints will be analyzed using log rank tests. Results will be expressed in terms of median survival times per group, hazard ratios, and p-values.
- 8.4.2 For quality of life, a linear mixed model will be used to test the association between quality of life score and the factors including treatment, AF burden and time. Results will be expressed in terms of p-values.
- 8.4.3 The continuous variables will be summarized using descriptive statistics (mean, standard deviation, median, range) and comparisons between the randomization groups will be performed using ANOVA, and equivalent non-parametric method, Kruskal-Wallis test, will be used in case the assumption for ANOVA is violated. Normality of data will be checked with the aid of box plots, normal quartile plots, and normality tests. Results will be expressed in terms of p-values.
- 8.4.4 All categorical data will be presented using frequencies and percentages, and the comparisons between the randomization groups will be performed using chi-square tests if each cell in the contingency table has an expected frequency of five or more. If this is violated, Fisher's exact test will be used instead. Results will be expressed in terms of p-values.

## 9 PROTOCOL DESCRIPTION

### 9.1 PROTOCOL PROCEDURES - OVERVIEW

Table 1 – Protocol Procedure Overview

These activities are applicable to all patients regardless of randomization group.

(\*) This is **only to be performed when applicable**.

	When	Window	Activities
Enrollment	Within 30 days before or during Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Eligibility</li> <li>• Patient Informed Consent</li> </ul>
Baseline Visit	Within 60 days before Ablation Procedure	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Demographics &amp; Physical Examination</li> <li>• Patient Cardiovascular History</li> <li>• Patient Current Cardiac Medications</li> <li>• Patient Medical History</li> <li>• Patient AF History</li> <li>• 12 Lead ECG Information</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
Ablation Procedure	Within 60 days after Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Randomization</li> <li>• Ablation Procedure Data Collection</li> <li>• Adverse Events(*)</li> </ul>
1 <sup>st</sup> protocol follow-up	91 days after first Ablation Procedure (3 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events (*)</li> </ul>
Repeat Ablation Procedure	between day 91 – 183 (after first Ablation Procedure)	Not Applicable	<ul style="list-style-type: none"> <li>• Ablation Procedure Data collection</li> <li>• Adverse Events(*)</li> </ul>
2nd protocol follow-up	183 days after first Ablation Procedure (6 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
3rd protocol follow-up	274 days after first Ablation Procedure (9 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events(*)</li> </ul>



	When	Window	Activities
4th protocol follow-up	364 days after first Ablation Procedure (12 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
5th protocol follow-up	547 days post first Ablation Procedure (18 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>

## 9.2 ADVERSE EVENTS

### 9.2.1 Definition of Adverse Event, Adverse Device Effect, Serious Adverse Event and Serious Adverse Device effect according to ISO 14155:

9.2.1.1 **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation patient.

9.2.1.1.1 This definition does not necessarily imply that there is a causal relationship between the adverse event and the device under investigation.

9.2.1.2 **Adverse Device Effect (ADE)** is defined as any untoward and unintended response to a medical device.

9.2.1.2.1 This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. It also includes any event that is a result of a user error.

9.2.1.3 **Serious Adverse Event (SAE)** is defined as an adverse event that:

9.2.1.3.1 Led to death;

9.2.1.3.2 Led to a serious deterioration in the health of a patient that:

- Resulted in a life threatening illness or injury;
- Resulted in a permanent impairment of a body structure or a body function;
- Required in-patient hospitalization or prolongation of existing hospitalization; and
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

9.2.1.3.3 Led to foetal distress, foetal death or a congenital abnormality or birth defect.

9.2.1.4 **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

### 9.2.2 List of Anticipated Adverse Events and Adverse Device Effects:

9.2.2.1 The following represents a list of anticipated Adverse Events (AE) and Adverse Device Effects (ADE) experienced in either animal and/or clinical studies to date with AF ablation procedures, or reported in instructions for use and literature. Possible Adverse

Events (AE) and Adverse Device Effects (ADE) include but are not limited to the following:

Table 2 –Possible Adverse Events and Adverse Device Effects

Cardiac Events	Non-cardiac Events
<ul style="list-style-type: none"> <li>• Abnormal ECG</li> <li>• Angina (chest pain)</li> <li>• Arrhythmia</li> <li>• AV fistula</li> <li>• Complete heart block</li> <li>• Coronary artery injury</li> <li>• Cardiac Perforation</li> <li>• Cardiac Thromboembolism</li> <li>• CHF exacerbation – fluid overload</li> <li>• Component damage to ICD or implantable pacemaker</li> <li>• Death</li> <li>• Dislodgement of implantable cardioverter defibrillator or permanent pacing lead.</li> <li>• Endocarditis</li> <li>• Exacerbation of pre-existing atrial fibrillation</li> <li>• Heart Failure</li> <li>• Hypotension</li> <li>• Inadvertent AV block (complete heart block)</li> <li>• Left atrial / esophageal fistula</li> <li>• Myocardial infarction</li> <li>• Obstruction/perforation/damage of the vascular system</li> <li>• Palpitation</li> <li>• Pericardial effusion/cardiac tamponade</li> <li>• Pericardial effusion without tamponade</li> <li>• Pericarditis</li> <li>• Pulmonary vein dissection</li> <li>• Pulmonary vein stenosis</li> <li>• Pulmonary vein thrombus</li> <li>• Temporary or complete heart block</li> <li>• Unintended (in)complete AV, sinus node, heart block/damage</li> <li>• Vessel wall/valvular damage or insufficiency</li> <li>• Ventricular arrhythmia requiring defibrillation</li> </ul>	<ul style="list-style-type: none"> <li>• Air embolism</li> <li>• Anesthesia reaction</li> <li>• Cerebrovascular accident</li> <li>• High creatinine phosphokinase (CPK)</li> <li>• Infections</li> <li>• Local hematomas / ecchymosis</li> <li>• Laceration</li> <li>• Phrenic nerve damage</li> <li>• Pneumonia</li> <li>• Pneumothorax</li> <li>• Pulmonary edema</li> <li>• Pulmonary embolism</li> <li>• Pulmonary hypertension</li> <li>• Pleural effusion</li> <li>• Pseudoaneurysm</li> <li>• Respiratory depression</li> <li>• Skin burns</li> <li>• Syncope</li> <li>• Transient ischemic attack</li> <li>• Vasovagal reactions</li> </ul>

### 9.2.3 Procedure for Recording and Reporting Adverse Events

9.2.3.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation, regardless of the randomization group.

9.2.3.2 Safety surveillance and reporting starts at the time when the patient is enrolled into the investigation (date of signature of the informed consent) until the last investigational visit has been performed, or the patient has died, or the patient concludes his participation into the study.

9.2.3.2.1 **All Serious Adverse Events** and **all Unexpected Adverse Device Effects** are to be documented and reported to the sponsor **immediately**.

9.2.3.2.2 **Non-Serious Adverse Events** documentation and reporting are limited to cardiovascular and neurovascular events. Within cardiovascular, all arrhythmias that require medical assessment and/or intervention should be documented as an adverse event.

9.2.3.3 Should an AE occur, record AE information in the hospital records, document the information into the Adverse Event case report form (CRF) as soon as possible. By completing the CRF the sponsor will be notified.

9.2.3.3.1 Refer to appendices “Data Collection” and “Data Collection Method”.

9.2.3.3.2 Access the eCRF application.

9.2.3.3.3 Select the visit the AE is related to or indicate it as unscheduled visit.

9.2.3.3.4 Enter adverse event information into the **AE Notification** section of the CRF.

- Date the AE occurred;
- Date the center investigator or delegate became aware of the AE;
- Main complaints/symptoms of the AE;
- Initial diagnosis of the AE;
- Potential cause of the AE;
- Pre-existing medical conditions related to the AE;
- Seriousness of the AE;
- Device relationship to AE; and
- Status of the AE.

9.2.3.3.5 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

- 9.2.3.3.6 The CRF must be authorized by the principal investigator or delegated co-investigator.
- 9.2.3.3.7 As soon as the final details are available for the adverse event, the information should be reported on the AE Follow-Up section of the CRF.
- 9.2.3.3.8 Access the eCRF application.
- 9.2.3.3.9 Edit AE CRF, document information into the **AE Follow-Up** section of the case report form.
- Hospitalization details (if applicable);
  - Diagnostic test information (if applicable);
  - Treatment given (if applicable);
  - Final medical diagnosis & cause;
  - Patient condition;
  - Final AE status;
  - Seriousness of AE based on final medical diagnosis and cause;
  - Relationship of AE to device based on final medical diagnosis & cause.
- 9.2.3.3.10 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.
- 9.2.3.3.11 The CRF must be authorized by the principal investigator or delegated co-investigator.
- 9.2.3.4 Additional information will be requested, if necessary, by the Sponsor for reporting of AEs to regulatory authorities.
- 9.2.3.5 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

**NOTE:** If an adverse event is documented at the patient's last follow up visit (18 months), both the notification and follow-up information on the AE CRF are to be provided to the sponsor.

Pre-existing cardiac conditions that require planned hospitalization are not to be considered as AE

## 9.3 PATIENT DEATH

### 9.3.1 Procedure for Recording and Reporting Patient Death

9.3.1.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation, regardless of the randomization group.

9.3.1.2 Safety surveillance and reporting starts at the time when the patient is enrolled into the investigation (date of signature of the informed consent) until the last investigational visit has been performed.

9.3.1.2.1 All **Patient Deaths** are to be documented and reported to the sponsor **immediately**.

9.3.1.3 Should death occur, record death information in the hospital records, **immediately** document the information in the Death case report form (CRF). By completing the CRF the sponsor will be notified..

9.3.1.3.1 Refer to appendices “Data Collection” and “Data Collection Method”.

9.3.1.3.2 Access the eCRF application.

9.3.1.3.3 Select the visit the patient death is related to or indicate it as visit unscheduled visit.

9.3.1.3.4 Enter patient death information into the Patient Death CRF.

- Date the death occurred;
- Date the center investigator or delegate became aware of the death;
- Place where death occurred (e.g. hospital, nursing home, patient’s home);
- If death was witnessed;
- If autopsy was performed;
- Temporal cause of death
- Primary cause of death;
- Details regarding death; and
- If details of serious adverse event associated to the death are known by the center/investigator/delegate.

9.3.1.3.5 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

9.3.1.3.6 The CRF must be authorized by the principal investigator or delegated co-investigator.

- 9.3.1.4 Patient death may be an outcome of a serious adverse event (SAE).
  - 9.3.1.4.1 If the death is related to a SAE, all the efforts to get SAE details should be made and the Adverse Event CRF must be completed.
- 9.3.1.5 Patient death is an early conclusion to the patient's participation in the investigation. Complete Termination CRF.
- 9.3.1.6 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

## 9.4 EARLY CONCLUSION TO PATIENT PARTICIPATION

- 9.4.1 All reasonable efforts should be made to retain the patient in the clinical investigation until completion of the clinical investigation.
- 9.4.2 If a patient concludes their participation in the investigation, the patient's future management will not be changed by this decision, whether it is voluntary or otherwise,
- 9.4.2.1 A patient/family member may request to withdraw from the investigation at any time; She/he would be able to do so without having to justify it and without affecting her/his relationship with the investigator.
- 9.4.2.2 A patient dies. Refer to section 9.3, "Patient Death"; or
- 9.4.2.3 An investigator may withdraw a patient from the investigation at any time if she/he thinks it is in the patient's best interest; or
- 9.4.2.4 A investigator may withdraw a patient, if the patient does not come for their scheduled visits and/or is not compliant with the regimen of the protocol. This patient will be considered "lost to follow-up"; A patient will be considered "lost to follow-up" when 3 attempts to contact the patient were unsuccessful: A minimum of 2 documented phone calls by a physician/delegate to the patient/emergency contact and a certified letter sent to the last known address.
- 9.4.2.5 The Investigation is temporarily stopped or terminated, either at the local, national or international level, at the request of Ethics Committees, Competent Authorities, Departments of Health or the investigation Sponsor.
- 9.4.3 Should a patient withdraw and conclude participation in the investigation, document the information in the Termination case report form (CRF) as soon as possible. By completing the CRF the sponsor will be notified.
- 9.4.3.1 Refer to appendices "Data Collection" and "Data Collection Method".
- 9.4.3.2 Access the eCRF application.
- 9.4.3.3 Select the visit the patient death is related to or indicate it as visit unscheduled visit.
- 9.4.3.4 Enter patient early conclusion information into the Termination CRF.
- Date the early conclusion occurred; and
  - Reason for the early conclusion;
- 9.4.4 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.
- 9.4.5 The CRF must be authorized by the principal investigator or delegated co-investigator.



## 9.5 DEVIATIONS

- 9.5.1 Investigators are required to adhere to the Investigational Plan, signed Investigator's Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate Ethics Committees or applicable regulatory authorities.
- 9.5.2 A **Deviation** is defined as a situation in which there is a non-compliance with the protocol.
- 9.5.3 Anticipated deviations:
- 9.5.3.1 Patient Informed Consent is not approved by Ethics Committee;
- 9.5.3.2 Patient Informed Consent is not sign and/or date by the patient and/or investigator;
- 9.5.3.3 Study specific procedure was performed before the Patient Informed Consent was signed and dated by patient;
- 9.5.3.4 Investigational Required Visit not performed;
- 9.5.3.5 Investigational Required Visit performed outside the window;
- 9.5.3.6 24 hour Holter not performed/ data corrupted and not available;
- 9.5.3.7 ECG not performed/ data corrupted and not available;
- 9.5.3.8 Patient crossover from assigned randomization group; and
- 9.5.3.9 Repeat ablation performed out of the repeat ablation window (3 – 6 months).
- 9.5.4 Should a deviation occur, document the information in the Deviation case report form (CRF). By completing the CRF the sponsor will be notified.

**NOTE:** When a deviation occurs after enrollment for **patient consent**, record the information in the hospital record, **immediately** document the information in the Deviation and Termination case report form (CRF). By completing the CRF the sponsor will be notified.

Refer to appendices "Data Collection" and "Data Collection Method".

Access the eCRF application.

Select the scheduled or unscheduled visit the deviation is related to.

Enter deviation information into the Termination CRF.

- Date of deviation
- When the deviation occurred
- Type of deviation
- Medical justification

Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

The CRF must be authorized by the principal investigator or delegated co-investigator.

When a deviation occurs after enrollment for **patient eligibility**, record the information in the hospital record, **immediately** document the information in the Deviation case report form (CRF). By completing the CRF the sponsor will be notified. All the efforts should be made to keep the patient in the study.

The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

## 9.6 ENROLLMENT

- 9.6.1 Enrollment activities are performed after patients are screened and may occur prior to or at the same time as the baseline visit.
- 9.6.2 The site should maintain a Patient Screening Log, accounting for the patients who are and are not eligible for the investigation.
- 9.6.3 A patient who meets the inclusion criteria and does not meet the exclusion criteria is eligible to participate in the investigation.
  - 9.6.3.1 If a patient does not meet inclusion or meets exclusion criteria cannot participate in the investigation.
    - 9.6.3.1.1 Record enrollment information (consent and inclusion/exclusion) in the hospital records, complete the Enrollment and Termination Case Report Forms. The CRF must be authorized by the principal investigator or delegate.
    - 9.6.3.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

- 9.6.4 Inform the eligible patient about the investigation and provide the written consent to the patient.
- 9.6.4.1 The process of obtaining written consent from an eligible patient needs to comply with the Declaration of Helsinki, International Standards Organization (ISO) 14155-1 and applicable local laws and regulations.
- 9.6.5 Obtain the signature and date from the eligible patient on the ethics committee (EC) approved informed consent.
- 9.6.5.1 If the eligible patient cannot sign and date the EC approved informed consent him/herself then refer to ISO 14155-1 regarding alternatives for obtaining signature on the informed consent.
- 9.6.5.2 If an eligible patient does not sign and date the informed consent s/he cannot participate in the investigation. No further protocol activities are performed.
- 9.6.6 Obtain the signature and date from the principal investigator or delegate on the ethics committee (EC) approved informed consent.
- 9.6.7 The patient is enrolled in the investigation when both the patient and investigator signed/dated the informed consent.
- 9.6.7.1 If there are deviations with regard to obtaining informed consent notify the EC/IRB appropriately.
- 9.6.8 Provide one original signed and dated copy by patient and the principal investigator or delegate to the patient
- 9.6.9 File the second original appropriately in the Investigator Study Binder (ISB).
- 9.6.10 Record enrollment information (consent and inclusion/exclusion) in the hospital records, complete the Enrollment Case Report Form. Every effort will be made to notify the sponsor within 5 working days of enrollment. The CRF must be authorized by the principal investigator or delegate.
- 9.6.10.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

## **9.7 BASELINE VISIT**

- 9.7.1 All Baseline activities are performed after patient is enrolled in the investigation and no more than 30 days prior to undergoing catheter ablation procedure.
- 9.7.2 The following information will be collected at the baseline visit either from hospital records or through patient interaction:
- 9.7.2.1 Patient Demographics & Physical Examination
- Collect the age;
  - Collect the gender;
  - Provide the most recent value (within the last month) of the patient height;

- Provide the most recent value (within the last month) of the patient weight; and
- Collect the blood pressure;

#### 9.7.2.2 Patient Cardiovascular History

- Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;
- Provide the most recent value (within the last month) of the left ventricular ejection fraction (LVEF) derived from echocardiography or gated nuclear studies; and
- Provide the most recent value of the left atrial size.

#### 9.7.2.3 Patient Cardiac Medication

- Identify the drug category of the cardiac medications the patient is taking currently; and
- Document the type of antiarrhythmic the patient was taking in the past to manage AF

NOTE: Patient enrolled should be refractory to at least to one antiarrhythmic medication.

#### 9.7.2.4 Patient Medical History

- Indicate the pre-existing cardiac conditions and cardiac procedures; and
- Indicate the non-cardiac medical conditions.

#### 9.7.2.5 Patient Atrial Fibrillation History

- Provide the date (year) the patient first experience AF;
- Provide the average duration of AF episodes;
- Provide the frequency of AF episodes;
- Provide the number of previous Cardioversion for atrial arrhythmias.
- Indicate if the patient experienced any arrhythmias other than AF.

#### 9.7.2.6 Quality of life assessment

- Both the SF-36 and the EQ-5D questionnaire need to be completed, signed and dated by the patient.
- Record the CCS SAF scale.

#### 9.7.2.7 ECG Information

- Provide the information of the most recent ECG performed (heart rate, rhythm on ECG, QT information, general findings).

- 9.7.2.8 Record baseline visit information in hospital records, complete the Baseline Case Report Forms. Every effort would be made to notify the sponsor within 14 days of the visit. The CRF must be authorized by the principal investigator or delegate.
- 9.7.2.9 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.7.3 Adverse Event (when applicable)
  - 9.7.3.1 Check if any adverse event or adverse device effect occurred.
  - 9.7.3.2 Report the adverse event according to specifications in section “Adverse Event”.

## **9.8 ABLATION PROCEDURE**

- 9.8.1 All patients will undergo catheter ablation using radiofrequency (RF) energy in the cardiac electrophysiology lab as per site practice.
  - 9.8.1.1 Antiarrhythmic medications will be stopped at least 5 half-lives prior to the procedure, except amiodarone, which will be stopped >8 weeks prior to the procedure.
    - 9.8.1.1.1 If antiarrhythmic medications will not be stopped nor amiodarone, this will not be considered as a protocol deviation.
- 9.8.2 Randomization
  - 9.8.2.1 Prior to the ablation procedure, randomize the patient. For the randomization instructions, refer to “Appendix Randomization Instructions”.
    - 9.8.2.1.1 In case the strategy as defined per randomization cannot be performed and a different strategy is used, record the cross over information in the hospital records and complete the Deviation Case Report Forms. The CRF must be authorized by the principal investigator or delegate.
    - 9.8.2.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 9.8.3 Ablation Procedure

- 9.8.3.1 All procedures will be performed via transseptal access to the Left Atrium (LA).
- 9.8.3.2 After transseptal access, patients should be anticoagulated with intravenous heparin to maintain an ACT of > 250 sec.
- 9.8.3.3 A multipolar diagnostic catheter (minimum 4 poles) will be placed in the Coronary Sinus (CS).
- 9.8.3.4 A circular mapping catheter (minimum 10 poles) should be used for both mapping and confirmation of pulmonary vein isolation.
- 9.8.3.5 Ablation will be performed using a market approved open irrigated-tip ablation catheter. In Table 3 the maximum authorized power and irrigation settings are shown. For power and irrigation settings please follow the catheter Instruction for Use (IFU) and the clinical practice.

Table 3 – Irrigated ablation catheter maximum authorized settings.

Irrigated Ablation Catheter Recommended Settings	
Maximum Power	40 W (*)
Maximum Flow Rate	30 mL/min
(*) Lower power settings are recommended on the posterior wall (25-35 W) to avoid the possibility of esophageal injury.	

- 9.8.3.6 Continuous impedance monitoring should be employed and RF should be discontinued if a >10 ohm impedance rise is observed.
- 9.8.3.7 All procedures will be guided using a Cardiac mapping System - Ensite NavX System, St. Jude Medical. The mapping system will be used to construct a three-dimensional reconstruction (shell) of the LA, the PV, the CS, and RA if required. As mapping catheters physicians can use the circular mapping and/or ablation catheters.

### 9.8.4 Ablation Strategies

- 9.8.4.1 A description of each of the three specific catheter ablation strategies is detailed in the following sections:
  - Wide Circumferential Pulmonary Vein Antrum Isolation (PVI) – “Trigger-Based Strategy”, please refer to section 9.8.6.
  - Combined PV Antral Isolation and Ablation of Complex Fractionated Electrograms (PVI+CFE) – “Trigger and Substrate-Based Strategy”, please refer to section 9.8.7.
  - Combined PV Antral Isolation and Empiric Linear Ablation (PVI+Lines) – “Trigger and Substrate-Based Strategy”, please refer to section 9.9.8.

### 9.8.5 Additional Ablation

9.8.5.1 Upon completion of the randomized ablation strategy (whether on the initial or repeat procedure), investigators have the option of either ablating any additional atrial tachycardias or flutters that may arise, or simply cardioverting the patient back to sinus rhythm. Performing a right atrial cavotricuspid isthmus line is allowed in any of the three randomization strategies and will be left to investigator discretion.

9.8.5.2 Any additional ablation lesions performed to treat those tachycardias should be documented in the Ablation Case Report Form.

9.8.5.2.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

9.8.5.3 Performing additional lesions that would involve creating lesions prescribed by one of the other arms of the study is strongly discouraged. For example, if the patient is randomized to PVI+CFE, performing either a roof or mitral line would be strongly discouraged and vice versa.

9.8.5.3.1 If CFE or linear targets (roof or mitral) are performed in an arm which does not include such strategies, complete a Deviation Case Report Form.

9.8.5.3.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 9.8.6 Wide Circumferential Pulmonary Vein Antrum Isolation (PVI) “Trigger-Based Strategy”

9.8.6.1 Through transseptal accesses, the circular mapping and ablation catheters will be advanced into the LA, followed by reconstruction of the LA, PV and CS anatomy using the EnSite NavX.

9.8.6.2 The ostia and the antra of the PV will be defined by:

- Examination of the 3D electroanatomical shell;
- Visualization of the catheter tip entering the cardiac silhouette;
- A decrease in catheter impedance monitored by RF generator;
- Appearance of an atrial potential; and
- Intracardiac echocardiography, when available.



- 9.8.6.3 The circular mapping catheter will then placed sequentially within each of the PV antra to record PV potentials. Circumferential RF lesions will then be placed at least 1-2 cm outside of the PV ostia to encircle and electrically isolate each of the PV antra while avoiding PV stenosis.
  - 9.8.6.3.1 Because of the narrow ridge of tissue between the anterior aspect of the left superior PV and the left atrial appendage, ablation will be allowed within 1 cm of the ostium of the left superior PV to encircle and isolate this vein.
- 9.8.6.4 As each antrum is encircled, the circular mapping catheter should be used to confirm electrical isolation. Isolation of the PV antrum will be considered complete when all PV potentials within each antrum are abolished, as recorded by the circular mapping catheter.
  - 9.8.6.4.1 Ablation tags should only be placed on the LA reconstructed anatomy if RF energy is applied for more than 15 seconds at a given point.
- 9.8.6.5 During PVI ablation, the mean atrial fibrillation cycle length (AFCL) and AF regularity should be measured from a selected CS recording pre-ablation (baseline measurement) and post-ablation.
  - 9.8.6.5.1 The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and dividing 15000 by x.
  - 9.8.6.5.2 The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during ablation should be recorded.
  - 9.8.6.5.3 No intravenous antiarrhythmics should be used during ablation to change AFCL or help regularize/terminate AF.
- 9.8.6.6 If the patient is still in AF at the end of the procedure, electrical cardioversion should be performed to restore sinus rhythm.
  - 9.8.6.6.1 All of the PV antra should be rechecked in sinus rhythm to confirm electrical isolation. If complete isolation has not been achieved, further ablation may be performed to achieve this endpoint.
- 9.8.6.7 Rechecking of each of the PV antra should be performed at the end of the ablation procedure to confirm the presence of block after a minimum 20 minute wait after the last ablation lesion applied to that specific antrum.
  - 9.8.6.7.1 The endpoint is to achieve complete entrance and exit block of all PV antra as recorded by the circular

mapping catheter during sinus rhythm or CS pacing. Exit block should be determined by pacing at high output within the PV and looking for any conduction getting out into the LA. If there is no PV to LA conduction, or capture cannot be obtained anywhere inside the PV, then exit block is fulfilled.

9.8.6.7.2 Termination and/or non-inducibility of AF are not endpoints of this procedure.

9.8.6.8 If the patient is in atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. However, ablation of continuous fractionated electrograms (CFE) and creation of a mitral or roof line are strongly discouraged. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

9.8.6.8.1 If either CFE or mitral/roof lines have been ablated, complete the Deviation Case Report Form.

9.8.6.8.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

9.8.7 Combined PV Antral Isolation and Ablation of Complex Fractionated Electrograms (PVI+CFE) “Trigger and Substrate-Based Strategy”

9.8.7.1 Patients randomized to this arm will first undergo wide circumferential PVI as described in Section 9.8.6. The endpoint will be complete isolation of all four PV antra as detailed above.

9.8.7.2 Following completion of the PVI procedure, if the patient is in AF, further mapping will be performed to identify regions of CFE with the use of an automated mapping algorithm (EnSite Complex Fractionated Electrograms Algorithm – CFE, St. Jude Medical).

9.8.7.3 Following completion of the PVI procedure, if the patient is not in AF, AF should be induced by rapid atrial pacing from the distal tip of the CS catheter. Pacing should be performed at the shortest 1:1 atrial capture rate for up to 15 seconds at a time, up to 5 times in a row, with 30 seconds between attempts.

9.8.7.3.1 If AF cannot be sustained for longer than 1 min, an infusion of isoproterenol (causing an increase in baseline heart rate > 50%, dose up to 10 mcg/min) can be used to sustain AF. Induced AF must persist for >1 minute prior to mapping for CFE.

9.8.7.4 Once in AF, CFE mapping using the automated algorithm will be performed in the LA, CS, and RA (if needed).

9.8.7.4.1 EGMs should be obtained during AF by mapping with the circular mapping catheter. In areas where the

circular mapping catheter cannot obtain good atrial contact, mapping may be supplemented using the 4 mm tip ablation catheter. Bipolar recordings are to be filtered at 30-300 Hz (default value).

- 9.8.7.5 The detailed technique for mapping/ablating CFE using the automated algorithm has been described and validated previously. In brief, the algorithm measures the time between multiple, discrete deflections (-dV/dT) in a local AF electrogram (EGM) recording over a specified length of time (5 sec) and then averages these inter-deflection time intervals to calculate a mean cycle length (CL) of the local EGM during AF. This mean CL is then projected onto the LA anatomical shell as a color-coded display. The shorter the CL, the more rapid and fractionated the local EGM. Specifically for this study, regions with a mean CL of less than 120 ms will be defined as “CFE” based on previously published data<sup>14</sup>.
- 9.8.7.6 The recommendations and settings for EnSite Complex Fractionated Electrograms Algorithm – CFE is reported in Table 4. If the recommendations and settings are not followed, it is not necessary to complete a Protocol Deviation
- 9.8.7.6.1 At the start of the procedure, the baseline signal noise level should be determined and the P-P Sensitivity limit is to be set just above the noise level (typically 0.03-0.05 mV) to avoid noise detection while allowing detection of low amplitude CFE (often <0.5 mV).
- 9.8.7.6.2 Selectable peak to peak EGM amplitude, EGM width, and post-EGM refractory period are defined to assist in algorithm deflection detection
- 9.8.7.6.3 Width Value and Refractory Value are typically set at 15-20 ms and 35-45 ms respectively to avoid detection of far-field EGMs and to avoid double-counting individual EGM deflections.
- 9.8.7.6.4 To avoid including signals from bipoles that are internal in the LA, the Interpolation Value of the algorithm should be adjusted (no more than 8 mm) to include only those signals obtained from bipoles with good atrial shell contact. CFE sites defined by the algorithm (CL < 120 ms) will be targeted for ablation. Regions with the shortest CL should be targeted first, followed by longer CL regions (up to 120 ms). Ablation at a CFE site shall be continued until the local EGM is eliminated which typically requires 20-60 sec of RF application.
- 9.8.7.7 During ablation of CFE sites, the mean atrial fibrillation cycle length (AFCL) and AF regularity should be measured from a selected CS recording. The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and

dividing 15000 by x. The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during CFE ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during CFE ablation should be recorded. No intravenous antiarrhythmics should be used during CFE ablation to change AFCL or help regularize/terminate AF.

- 9.8.7.8 The endpoint for CFE ablation is:
- Elimination of all CFE sites in the LA, CS and RA, or
  - AF termination.
- 9.8.7.9 Initially, all CFE sites in the LA and CS should be targeted. If AF does not terminate, CFE in the RA should be mapped and ablated.
- 9.8.7.10 If AF still does not terminate, sinus rhythm may be restored by electrical cardioversion
- 9.8.7.11 If AF terminates to sinus rhythm, any remaining unablated CFE sites do not need to be ablated.
- 9.8.7.12 If AF terminates to an atrial flutter/tachycardia, all remaining CFE sites should be ablated.
- 9.8.7.13 If AF terminates to an atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.
- 9.8.7.14 However, creation of a roof or mitral line, as outlined in the PVI+Lines strategy, is strongly discouraged.
- 9.8.7.14.1 If either a mitral or roof line is performed in this randomization arm, complete a Deviation Case Report Form.
- 9.8.7.14.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.8.7.15 At the very end of the CFE procedure, in sinus rhythm, investigators should place the circular mapping catheter into each of the PV antra to confirm ongoing entrance block and exit block at least 20 min after the last ablation performed in the PVs. If there is PV reconnection, further ablation may be performed to achieve PV antral isolation and to achieve the endpoint of entrance and exit block.

Table 4 - Recommendations and Settings for EnSite CFE Algorithm

As CFE mapping catheter use the circular mapping catheter or ablation catheter in regions where the circular mapping catheter has poor contact. The circular mapping catheter is preferable. Its electrodes size and electrodes spacing allow increasing the signal quality.		
Assess the baseline noise using the callipers of the DX Landmarking Tools		
Parameter	Value	Parameter definition
P-P Sensitivity	0.03-0.05 mV (Just above the baseline noise)	The P-P Sensitivity control is a minimum peak-to-peak voltage required for the detection algorithm to operate. Incoming signals must be larger than the P-P Sensitivity in order to be considered activation by the system.
Width value	15-20 ms	The Width slider controls the minimum complex width to consider for activation. As CFE maps always use -dV/dt detection type, this parameter indicates the width of the most negative slope. This setting will avoid detection of far-field smooth deflection.
Refractory value	35-45 ms	The Refractory slider controls the minimum amount of time between detections, in order to avoid over counting a single EGM with multiple components.
EGM Segment Length	min 5 s	The Segment Length indicates the total recording duration at each point.
Interpolation value	4-8 mm	The Interpolation slider controls the minimum distance between surface points necessary for the system to interpolate color.
Interior Projection Exterior Projection	4-8 mm	Interior and Exterior Projection are projection sliders that control the Maximum/minimum distance that a 3D Point can project to a location on the interior geometry surface. This setting will avoid collection of EGMs from electrodes that are not in good contact with map shell
Auto-color	ON	The Auto Color toggle controls whether the system automatically controls the pointers on the color bar during DX Landmarking. If Auto Color is enabled, the pointers will adjust to the minimum and maximum data values for all points in the current map.
Set the color-slider so that the orange-red transition occurs around 120 ms. All regions < 120 msec will be considered "CFE" region. Those region will appear red or white.		
Confirm accuracy of regions labeled as "CFE" by checking EGMs visually		
Target all red-white regions for ablation. This will often require several lesions over "islands" of CFE throughout the atrium. Try to target white spots (the shortest CL) first.		
If CFE ablation in the LA and CS do not terminate AF, map and ablate CFE in the RA.		

### 9.8.8 Combined PV Antral Isolation and Empiric Linear Ablation (PVI+Lines) “Trigger and Substrate-Based Strategy”

9.8.8.1 Patients randomized to this arm will first undergo wide circumferential PVI as described in Section 9.8.6. The endpoint will be complete isolation of all four PV antra as detailed above.

9.8.8.2 Following successful completion of PVI, the patient will undergo empiric linear ablation assisted by the Ensite NavX.

9.8.8.3 All patients randomized to this strategy will undergo ablation of:

- A roof line. Description of the recommended roof line ablation technique is reported in section 9.8.8.7.
- Mitral isthmus line (either posterior or anterior approach). Description of the recommended mitral isthmus line ablation technique is reported in section 9.8.8.8.

9.8.8.4 In general, the use of a stabilizing sheath is suggested to achieve good catheter contact and stability along the path of the linear ablation. Lines can be performed by rotating the sheath (clockwise or counterclockwise) with slight deflection of the catheter. At each point, a minimum of 30 sec of RF should be delivered to achieve local EGM elimination or formation of local double potentials. The catheter can then be moved within 5 mm to the next site on the line.

9.8.8.5 The goal of all linear lesions will be to achieve complete block. Conduction block can only be assessed in sinus rhythm, so cardioversion will be required for testing after the lines are made. If a conduction gap in the line cannot be closed, lesions applied off the line, but adjacent to it, can often close the gap. All lesions do not need to fall exactly on the line. Description of conduction block recommended techniques both for Roof Line and Mitral Isthmus are reported in sections 9.8.8.9. Conduction block should be assessed at least 20 min after the last ablation lesion along the line.

9.8.8.6 During linear ablation, the mean AFCL and AF regularity should be measured from a selected CS recording at baseline and after each line is completed. The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and dividing 15000 by x. The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during ablation should be recorded. No intravenous antiarrhythmics should be used during ablation to change AFCL or help regularize/terminate AF.

#### 9.8.8.7 **Roof Line recommended ablation technique.**

9.8.8.7.1 The goal of the roof line is to connect the superior margins of both superior PVs with a line as cranial as

possible. The line may be performed from left to right or right to left.

9.8.8.7.2 The recommended technique is to have the ablation catheter almost entirely inside the sheath with the distal and proximal poles extending outside of it. The sheath can then be used to position the catheter tip at the margin of the left superior PV lesion set. By dragging the catheter along the roof with gentle clockwise rotation of the sheath, lesions can be delivered, usually with a perpendicular catheter-tissue interface.

9.8.8.7.3 Caution should be exercised to avoid perforation with excessive pressure or power.

#### 9.8.8.8 **Mitral Isthmus Line recommended ablation technique.**

9.8.8.8.1 The mitral isthmus line should be performed using either a posterior or anterior approach.

9.8.8.8.2 **Posterior approach;** the goal is to create a line from the lateral mitral annulus (MA) to the left inferior PV ostium. The catheter is extended through the sheath to the lateral MA (typically close to the distal CS poles) where there is a signal with an A:V ratio of 1:1 or 2:1. The catheter-sheath assembly is then rotated clockwise typically with a perpendicular catheter-tissue interface. The lesions are delivered with clockwise rotation until the left inferior PV ostium is reached. Up to 70% of patients will require ablation within the distal CS to achieve complete block across the MA when using the posterior approach. If block is not achieved, the ablation catheter may be placed in the distal CS. To avoid perforation & circumflex coronary damage, the catheter should be deflected upwards towards the atrial side and power should be limited to 20-25 W. Maximum catheter power settings are reported in Table 4.

9.8.8.8.3 **Anterior approach;** the goal is to create a line from the superior aspect of the MA to the left superior pulmonary vein and/or roof line. Using counter clockwise rotation of the sheath-catheter assembly, the catheter can maintain good anteroseptal wall contact and a line can be created from the MA to the roof line. An anterior approach may also help achieve block when the posterior approach fails.

#### 9.8.8.9 **Pacing Manoeuvres to assess conduction block**

9.8.8.9.1 Once the lines are completed, the patient should be cardioverted and assessment of conduction block should occur at least 20 minutes after the last ablation lesion along the line. In general, pacing from the CS should reveal widely separated double potentials along each of the lines. Single potentials or closely-spaced

potentials with fractionated activity indicate potential gaps and require further ablation.

- 9.8.8.9.2 To assess the **block across the roof line** can be confirmed by demonstrating that the activation sequence of the posterior LA is caudocranial instead of craniocaudal. This can be shown by pacing from the left atrial appendage. If the ablation catheter is placed on the low posterior LA, the pace to local EGM delay will be less than when the ablation catheter is placed in the high posterior LA, closer to the roof line. In the case where the roof line is assessed after creation of a line of block at the mitral annulus, activation of the posterior LA occurs not only low to high, but also right to left (pacing in LAA). Again, you can show this by demonstrating a shorter pace to EGM delay on the right posterior LA compared to the left posterior LA.
- 9.8.8.9.3 To assess the **block across a posterior mitral line**, pacing lateral to the line in the LA appendage from the ablation catheter should result in a proximal-distal activation sequence along the CS. With the ablation catheter still lateral, pacing from the proximal CS should result in a delayed activation in the ablation catheter (usually more than 90-100 msec).
- 9.8.8.9.4 To assess the **block across an anterior mitral line**, place the pacing catheter just lateral to the line and the circular mapping catheter on the high septum, medial to the ablation line. Pacing from the ablation catheter will result in lateral and posterior propagation around the MA with delayed activation in the high septum. As the ablation catheter is moved more laterally, the conduction delay to the septum should shorten. Alternatively, complete linear block can be confirmed if pacing laterally to the line results in a distal to proximal CS activation pattern, while after dragging the catheter to the septal side of the line, the CS is activated from proximal to distal.
- 9.8.8.10 If complete linear block cannot be achieved using a given approach along the mitral annulus, the other approach should be attempted.
- 9.8.8.11 If complete linear block cannot ever be achieved along either line, despite the investigator's best efforts, then this should be documented in the Ablation Case Report Form. This, however, would not be considered a protocol deviation.
- 9.8.8.12 If the patient is in atrial flutter or tachycardia, and the the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and



nature of the additional lesions and/or the cardioversion should be recorded and documented.

9.8.8.13 However, mapping and ablation of CFE in this arm are strongly discouraged. If CFE ablation is performed in this arm, complete a Deviation Case Report Form.

9.8.8.14 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

9.8.8.15 At the very end of the PVI+Lines procedure, in sinus rhythm, investigators should place the circular mapping catheter into each of the PV antra to confirm ongoing entrance block and exit block at least 20 min after the last ablation in the PVs. If there is PV reconnection, further ablation may be performed to achieve PV antral isolation to achieve the endpoint of entrance and exit block.

#### 9.8.9 Post Ablation Activities

##### 9.8.9.1 Anticoagulation therapy

9.8.9.1.1 All patients will remain anticoagulated with warfarin to maintain an INR of 2-3, or a direct antithrombin inhibitor, for a minimum of 3 months post-ablation.

##### 9.8.9.2 Antiarrhythmic medications

9.8.9.2.1 Antiarrhythmic medications may be continued for the first 3 months following the first ablation to avoid early recurrences. At 3 months, antiarrhythmics must be stopped to assess for clinical recurrence.

9.8.9.2.2 The decision to use antiarrhythmics for the first three months, and the choice of drug, will be left to the discretion of the investigator. However, use of amiodarone for these first three months will not be allowed in the protocol given the long half-life of this medication and the potential for interfering with endpoint assessment at follow-up visits after three months.

- 9.8.10 Record ablation information in hospital records and complete the Ablation Case Report Forms. The CRF must be authorized by the principal investigator or delegate.
  - 9.8.10.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.8.11 Collect EnSite NavX study records on a disk, regardless of randomization group. Before copying the disk, make sure that the patient information will not be displayed. To copy the study records to a disk refer to the EnSite System IFU. Patient ID number needs to be reported on the procedure CD/DVD label.
- 9.8.12 Adverse Event (when applicable)
  - 9.8.12.1 Check if any adverse event or adverse device effect occurred.
  - 9.8.12.2 Report the adverse event according to specifications in section “Adverse Event”.

## 9.9 REPEAT ABLATION PROCEDURES

- 9.9.1 The repeat ablation procedure should employ the identical strategy to the randomized strategy employed during the first ablation procedure.
- 9.9.1.1 Failure to employ the initial randomized strategy for the repeat procedure will be considered a protocol deviation. In case the strategy as defined per randomization cannot be performed and a different strategy is used, record the cross over information in the hospital records and complete the Deviation Case Report Form. The CRF must be authorized by the principal investigator or delegate.
- 9.9.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.9.2 Blanking Period after the first ablation procedure
- 9.9.2.1 Based on previously published data<sup>8,11,12</sup>, early recurrence of atrial flutter and/or AF post-ablation may be common in the first 3 months after the procedure and may not predict long-term outcome. Therefore, a 3 month blanking period will be employed after the first procedure as per the HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation<sup>22</sup>. **During this blanking period, recurrences of AF/AT/AFI will not be counted and repeat procedures should not be performed any sooner than 3 months after the first ablation.** Any repeat procedures should be done between 3 and 6 months of the initial procedure.
- 9.9.2.1.1 If the repeat ablation procedure is not performed between month 3 and month 6, record the information in the hospital records and complete the Deviation Case Report Forms. The CRF must be authorized by the principal investigator or delegate.
- 9.9.2.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.9.2.2 During the first two months of the blanking period, it is recommended to treat the patient with antiarrhythmic medications.
- 9.9.2.2.1 If the patient will not be treated with antiarrhythmic medications this will not be considered as a protocol deviation.
- 9.9.2.3 If a patient has an early recurrence of atrial arrhythmia during the blanking period, it is recommended that the patient be cardioverted and see if arrhythmia consistently recurs before making a decision to perform another ablation.
- 9.9.2.3.1 If the cardioversion will not be performed this will not be considered as a protocol deviation.

### 9.9.3 Blanking period after the repeat ablation procedure

9.9.3.1 A 3 month blanking period will be employed after the repeat ablation procedure. During this blanking period, recurrences of AF/AT/AFI will not be counted as per the secondary endpoints.

9.9.3.2 During the first two months of the blanking period, it is recommended to treat the patient with antiarrhythmic medications.

9.9.3.2.1 If the patient will not be treated with antiarrhythmic medications this will not be considered as a protocol deviation.

9.9.3.3 If the patient has recurrence of atrial arrhythmia without being treated with antiarrhythmic medications, it is recommended that the investigator may cardiovert and/or start antiarrhythmic drug therapy.

9.9.3.3.1 If the patient will not be treated with antiarrhythmic medications and/or cardioversion will not be performed, this will not be considered as a protocol deviation.

### 9.9.4 Repeat ablation Procedure in the PVI randomization group

9.9.4.1 During the second procedure in the PVI arm, identification of conduction gaps between the PVs and LA should be identified. Gaps should be targeted for ablation to re-isolate the PV antra.

9.9.4.2 The goal should be to re-achieve complete isolation of all PVs from the LA as determined by both entrance and exit block.

9.9.4.3 If the patient is in atrial flutter or tachycardia, and the the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

9.9.4.4 However, performance of either CFE ablation or a mitral or roof line is strongly discouraged. If the patient has a mitral or roof dependent flutter, it is suggested that this may be cardioverted at the end of the procedure. If CFE or a mitral/roof line are performed, complete a Deviation Case Report Form.

9.9.4.4.1 Refer to "Appendix Data Collection" for access and information regarding patient data collected for this investigation.

### 9.9.5 Repeat ablation Procedure in the PVI + CFE randomization group

- 9.9.5.1 During the second procedure in the PVI+CFE arm, identification of conduction gaps between the PV antra and the LA should be identified and targeted for ablation as described above.
- 9.9.5.2 If the patient is not already in AF, AF should be re-induced to identify and ablate any regions of CFE. If CFEs cannot be identified in the LA, CS, or RA, the patient may be cardioverted back to sinus rhythm as during the first procedure.
- 9.9.5.3 If the patient is in atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.
- 9.9.5.4 However, performance of either a mitral or roof line is strongly discouraged. If the patient has mitral or roof dependent flutter, it is suggested that this may be cardioverted at the end of the procedure. If a roof/mitral line are performed, complete a Deviation Case Report Form.
  - 9.9.5.4.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 9.9.6 Repeat ablation Procedure in the PVI + Lines randomization group

- 9.9.6.1 During the second procedure in the PVI+Lines arm, identification of conduction gaps between the PV antra and the LA should be identified and targeted for ablation as described above.
- 9.9.6.2 Once PV isolation has been achieved, all of the lines should be checked for conduction gaps. Presence of these gaps may be confirmed by pacing manoeuvres as described in section 9.8.8.9. If conduction gaps are identified, the roof and the MA lines should be reinforced with additional ablation either along the line or immediately adjacent to it until block is achieved.
- 9.9.6.3 If the patient is in atrial flutter or tachycardia, and the the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.
- 9.9.6.4 However, performance of CFE ablation is strongly discouraged. If CFE ablation is performed, complete a Deviation Case Report Form.
  - 9.9.6.4.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

- 9.9.7 Repeat Ablation Procedure for Patients Presenting with Atrial Tachycardia or Flutter Only
- 9.9.7.1 For patients who return for a repeat ablation procedure who have only had recurrence of an atrial tachycardia or flutter, the culprit flutter and/or tachycardia may be targeted. However, the initial randomized strategy should also be repeated as well. Thus, isolation of the PVs should be confirmed and CFE and/or linear ablation should be repeated as applicable and as described in section 9.9.4, 9.9.5 and 9.9.6.
- 9.9.7.2 If a patient returns in mitral or roof dependent flutter in either the PVI or PVI+CFE arms, performance of a roof or mitral line is strongly discouraged. Every attempt would be made not to perform any mitral or roof line. If a mitral or roof line is performed, complete a Deviation Case Report Form.
- 9.9.7.2.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.9.7.3 Right atrial cavotricuspid lines may be performed in any of the three randomized strategies at any time and is left to investigator discretion.
- 9.9.8 Record the repeat ablation information in the hospital records, complete the Repeat Ablation Case Report Form (CRF). Every effort would be made to notify the sponsor within 14 days of the visit. The CRF needs to be authorized by the principal investigator or delegate.
- 9.9.8.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.9.9 Collect EnSite NavX study records on a disk, regardless of randomization group. Before copying the disk, make sure that the patient information will not be displayed. To copy the study records to a disk please refer to the EnSite System IFU. Patient ID number needs to be reported on the procedure CD/DVD label.
- 9.9.10 Adverse Event
- 9.9.10.1 As the repeat ablation procedure requires the patient to be hospitalized record the information in the hospital records and complete the Adverse Event Case Report Form. The CRF must be authorized by the principal investigator or delegate.
- 9.9.10.2 Check if any adverse event or adverse device effect occurred.
- 9.9.10.3 Report the adverse event according to specifications in section “Adverse Event”.
- 9.9.10.4 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

## 9.10 PROTOCOL REQUIRED FOLLOW-UP

9.10.1 Scheduled visits will occur at 3, 6, 9, 12, and 18 months after the first ablation procedure ( $\pm$  14 days for each time point for follow-up). The follow up will occur in the outpatient department of each participating institution.

9.10.2 The Follow Up schedule is summarized in Table 1.

9.10.3 The following information will be collected at the follow up visit either from hospital records or through patient interaction:

### 9.10.3.1 Physical Examination

- Collect the blood pressure;

### 9.10.3.2 Recurrence of atrial arrhythmias

- List the atrial arrhythmia episodes the patient experienced since the last visit;
- Classify the episodes; and
- Provide the duration of the episodes;

### 9.10.3.3 Patient Cardiac Current Medication

- Document a change in cardiac medication therapy since the last visit.

### 9.10.3.4 ECG Information

- Provide the information from ECG performed during the visit (heart rate, rhythm, QT information and other findings).

### 9.10.3.5 24 hour Holter

- List the atrial arrhythmia episodes collected by the 24 holter;
- Classify the episodes; and
- Provide the duration of episodes.

### 9.10.3.6 Quality of Life assessment

- Collect Quality of life measurements using the SF-36 and EQ-5D.
- Record the CCS SAF Scale...
- The quality of life measurement will be assessed at the 6, 12 and 18 months follow up visit.

- 9.10.4 Record the follow up information in the hospital records and complete the Follow Up Case Report Form (CRF). The CRF needs to be authorized by the principal investigator or delegate.
  - 9.10.4.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 9.10.5 Adverse Event (when applicable)
  - 9.10.5.1 Check with the patient if any adverse events or adverse device effect occurred since the last visit.
  - 9.10.5.2 Report the adverse event according to specifications in section “Adverse Event”.
- 9.10.6 Patient Death (when applicable)
  - 9.10.6.1 If the patient died before the visit took place, report it immediately to the sponsor as indicated in section “Patient Death”.
- 9.10.7 Early Withdrawal (when applicable)
  - 9.10.7.1 If the patient decides to withdraw from the investigation for whatever reason, report it immediately to the sponsor as indicated in section "Early conclusion to patient participation".



## **9.11 TRANS TELEPHONIC MONITORING**

- 9.11.1 Patients will be provided with a Trans Telephonic Monitor (TTM) to assess the heart rhythm for the entire duration of the follow-up period.
- 9.11.2 Patients will be asked to send transmissions:
  - 9.11.2.1 Once per week whether or not they are experiencing symptoms to assess for asymptomatic recurrences.
  - 9.11.2.2 Any time they feel any symptom(s) of arrhythmia.
- 9.11.3 If the patient has an implanted device (pacemaker, implantable defibrillator, implantable loop recorder), interrogation of the device will also be used to assess the patient's rhythm where applicable.
- 9.11.4 The TTM will be adjudicated independently by a Core Lab.

## **9.12 QUALITY OF LIFE ASSESSMENT**

- 9.12.1 Quality of life measurements will be performed at baseline, 6, 12, and 18 months after the ablation procedure.
- 9.12.2 The quality of life assessment will be done using the following questionnaires:
  - 9.12.2.1 The 36-item Short-Form Health Survey (SF-36).
  - 9.12.2.2 Euro-QoL 5D (EQ-5D).
- 9.12.3 The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale will be also assessed<sup>26</sup>. For the SAF scale, refer to Appendix L.

## **9.13 COST EFFECTIVENESS ASSESSMENT**

- 9.13.1 The cost effectiveness of the three ablation strategies will be assessed, refer to Secondary End Points section 4.2.1.19.
- 9.13.2 A unitary cost per country will be attributed to any hospitalization, repeat ablation procedure, intervention, diagnostic, drug therapy and consultation (GP and/or specialistic visits) that can be referred to the treatment of atrial fibrillation or and that are not required as per protocol.

## **10 RISK DESCRIPTION AND MINIMIZATION**

### **10.1 RISKS**

There is no data suggesting that the risks as reported in section 9.2 Adverse Events is any higher with one technique over the other. In fact, as shown in the STAR AF pilot study<sup>23</sup>, PVI+CFE approach was not associated with any increased risk over PVI alone. Even fluoroscopic exposure times and procedural times were not significantly different between the two arms.

## **11 INVESTIGATION ORGANIZATION**

### **11.1 INVESTIGATION MANAGEMENT**

#### **11.1.1 Sponsor**

The organization, which takes responsibility for the initiation and/or implementation and coordination for the investigation is SJM International, Inc, with offices located at:

St. Jude Medical Coordination Centre BVBA  
Corporate Village, Building Figueras  
Da Vincilaan, 11, Box F1  
B-1935 Brussels  
Belgium  
Tel: +32 2 774 69 37  
Fax: +32 2 774 69 46

The SJM International, Inc., will delegate responsibilities to the local SJM clinical entities in each country.

#### **11.1.2 Sponsor Responsibilities**

Sponsor's responsibilities are in accordance with applicable ISO 14155 guidelines.

It is the responsibility of St. Jude Medical, as the sponsor of the investigation to ensure proper monitoring and compliance with regulatory requirements.

This includes but is not limited to the following activities:

- Select the clinical investigators;
- Activate the study centers after receipt of the required documentation;
- Develop the study database, and perform the analysis;

- Sign off the clinical investigational plan before the start of the investigation or after modifications to the protocol;
- Reviewing collected data and investigation documentation for completeness and accuracy; and
- Ensure that all adverse events and adverse device effect are reported and reviewed with the clinical investigator(s) and where appropriate that all serious adverse events and serious adverse device effects are reported to the relevant authorities and Ethics Committee(s) and or safety monitoring committee(s).

Sponsor personnel or its delegates will not:

- Practice medicine;
- Provide medical diagnosis or treatment to patients;
- Discuss a patients' condition or treatment with a patient without the approval and presence of the health care Practitioner; and
- Independently collect critical study data.

## **11.2 CLINICAL COORDINATING INVESTIGATOR**

The clinical coordinating investigator appointed by St Jude Medical for the STAR AF II investigation is:

Atul Verma, MD FRCPC  
Staff Cardiology, Electrophysiology  
Southlake Regional Health Centre  
712 Davis Drive - Suite 105  
Newmarket, Ontario, Canada, L3Y 8C3  
Phone – 001 905 953 7917  
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## 11.3 INVESTIGATOR

An investigator is defined as an individual and/or institution responsible for the conduct of a clinical investigation who and/or which takes the clinical responsibility for the well-being of the subjects involved.

### 11.3.1 Investigator Responsibilities

This investigation will be conducted in accordance with applicable ISO 14155 guidelines, this clinical investigational plan, the signed Agreement, and other agreements applicable laws and regulations and any conditions of approval imposed by the Ethics Committee. To ensure compliance with the guidelines, the sponsor, and independent body, or a regulatory agency may audit the investigation.

By agreeing to this protocol, the investigators and their institutions accept to allow monitoring, audits, Ethics Committee and IRB review, and regulatory inspections that are related to the investigation. They also agree to provide authorized individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate patient consent and patient data confidentiality.

A principal investigator should have experience in and will be responsible for:

- Providing signed Investigator/Co-Investigator (s) Agreement.
- Providing appropriate Ethics Committees Approved Informed Consent.
- Conducting the clinical investigation in accordance with the signed agreement with St Jude Medical, the investigational plan, all applicable laws and regulations (e.g. ISO 14155) and any conditions of approval imposed by the appropriate Ethics Committees or applicable regulatory authorities where the investigation is performed.
- Collection and archiving of data obtained after implant and at follow-up examinations and after the investigation has been completed.
- Strict adherence to the Clinical Investigational Plan testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation.
- Screening and selecting appropriate patients.
- Support the monitor and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. The investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from St Jude Medical.

In addition to the responsibilities of the investigators, the study Coordinating Clinical Investigator will:

- Sign off the final version of the clinical investigational plan and after modifications to the protocol.
- Act as main contact for all study investigators in case of medical questions related to the conduct of the investigation.

### 11.3.2 Investigator Study binder

The investigator will be provided with an Investigator Study Binder (ISB) at the start of the investigation. This file contains all relevant documents necessary for the conduct of the investigation.

All centre data is forwarded to SJM and managed by the clinical project leader (CPL).

Table 5: Centre data collected

Centre Data Collected	Format
EC Approval of Protocol	Paper
EC Approved Patient Informed Consent.	Paper
EC Communication	Paper
Clinical Study Agreement and Exhibits A-E	Paper
Curriculum Vitae site Staff	Paper
Signature and delegation Log	Paper
Initiation Visit Log	Paper

### 11.3.3 Source Data and Patient Files

The investigator has to keep a written or electronic patient file for every patient participating in the clinical investigation. In this patient file, the available demographic and medical information of a patient has to be documented, in particular the following: name, date of birth, sex, height, weight, patient history, concomitant diseases and concomitant medication (including changes during the course of the investigation), statement of entry into the investigation, investigation identification, randomization number, the date of informed consent, all investigational visit dates, predefined performed examinations and clinical findings, observed AEs, and reason for withdrawal from the investigation, if applicable. It should be possible to verify the inclusion and exclusion criteria for the investigation from the available data in this file. It must be possible to identify each patient by using this patient file.

Additionally, any other documents with source data have to bear at least the patient identification and the printing date printed by the recording device to indicate to which patient and to which investigational procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator. All data recorded on the CRF must also be part of the patient's source data.

#### 11.3.4 Record Retention and Archiving

The ISB (Investigator Study Binder) must be safely archived after termination of the investigation.

It is the responsibility of the investigator to ensure that the patient identification logs are stored for at least 15 years beyond the end of the clinical investigation. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the Sponsor.

### **11.4 AMENDMENT PROCEDURE**

Major changes to the protocol will be described in a “CIP Amendment”. The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

The principal investigator will acknowledge the receipt of the amendment and confirm by their signature on the Amendment Signature page that they will adhere to the amendment.

The amendment must be submitted to the relevant EC/IRB and to authorities, where required. Approval from the EC/IRB will be required prior to implementation of the amendment. The approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to St. Jude Medical prior to implementation of the amendment.

Any amendment affecting the patient requires that the patient be informed of the changes and a new consent be signed and dated by the investigator and patient prior to the patient’s next follow-up.

Changes to, or formal clarifications of, the clinical investigational plan will be documented in writing and provided to investigators. This information will be incorporated when an amendment occurs.

### **11.5 BOARDS**

#### 11.5.1 Steering Committee

The STAR AF II Steering Committee is championed by the Coordination Clinical Investigator Dr. Atul Verma, MD FRCPC.

This committee will be actively involved in the investigation, and review its progress at regular intervals. At any time, this committee may request that the investigation be put on hold or even terminated for safety, ethical or other reasons.

#### 11.5.2 Data Safety Monitoring Board

A Data Safety Monitoring Board will be set up specifically to monitor safety data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically.

## 11.6 ETHICAL BASIS

This investigation will be performed in accordance with the World Medical Association Declaration of Helsinki (appendix C), ISO 14155 and all local legal and regulatory requirements.

Prior to start of the investigation, the clinical investigational plan will be submitted together with its associated documents (patient information sheets, patient informed consent forms in the local language) to the relevant Ethics Committee (EC) / Institutional Review Board (IRB) for review.

EC/IRB approval record should clearly identify

- the date of the meeting,
- constitution of the committee and voting members present at the meeting
- the approved version of the clinical investigational plan CIP
- the approved version of the patient information and informed consent.

Approval from the EC/ IRB is necessary prior to the start of the investigation. The original approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to St. Jude Medical prior to the first investigational assessment.

Any amendments to the protocol should be submitted to the relevant EC/IRB.

EC/IRB will be informed about SAEs and UADEs in accordance with local and national requirements.

## 11.7 INSURANCE

St. Jude Medical as Sponsor of this investigation has a general liability insurance for this investigation in accordance with the requirements of applicable local laws.

## 11.8 MONITORING

It is the responsibility of St Jude Medical as the sponsor of the investigation to ensure proper monitoring of the investigation and to ensure that the investigation is conducted, recorded and reported in accordance with the Clinical Investigational Plan, the signed Clinical Study Agreement, and the applicable laws and regulations.

Monitoring will be conducted at the centers participating in the investigation according to the standard operating procedures and work instructions.

### 11.8.1 Center Data

Center data will be reviewed for completion and regulatory compliance.

### 11.8.2 Patient Data

In line with ISO 14155 guidelines, monitoring will include verification of data entered in the CRF against original patient records. This verification will be performed with direct access to the original patient records. The Sponsor guarantees that patient confidentiality will be respected at all times. Participation in this investigation will be taken as agreement to permit direct source data verification.

Patient data will be reviewed for accuracy, quality and protocol adherence. Additionally patient safety will be evaluated.

### 11.8.3 Monitoring Activities

An overview of the monitoring activities is shown in Table 6.

Table 6 : Monitoring Activities

Visit Type	Prompted By	Scope of Visit	
Initiation	<ul style="list-style-type: none"> <li>○ Receipt of essential documents for centre by SJM</li> <li>○ Ethics Committee (EC) approval of Protocol</li> <li>○ EC approved Patient Informed Consent (PIC)</li> <li>○ Agreement plus exhibits completed, signed and dated by the centre</li> </ul>	No patient data	<ul style="list-style-type: none"> <li>○ Train staff participating in the investigation</li> <li>○ Collect outstanding center and staff documents</li> </ul>



Visit Type	Prompted By	Scope of Visit	
Periodic	<ul style="list-style-type: none"> <li>○ Enrollment of minimum, 3 patients at the centre</li> <li>○ Enrollment of greater than 10 patients at the centre</li> <li>○ Verification of critical data before database freeze and analysis</li> <li>○ Patient data quality issues identified at the centre</li> <li>○ Regulatory issues identified</li> <li>○ Safety Issues identified</li> </ul>	<ul style="list-style-type: none"> <li>○ Review patient's consent</li> <li>○ Review patient data as compared to source document</li> <li>○ Generate DCFs for missing and/or inaccurate patient data recorded on the CRFs</li> <li>○ Review adherence with the protocol</li> </ul>	<ul style="list-style-type: none"> <li>○ Resolve outstanding issues from previous monitoring visits</li> <li>○ Review ISB for completeness</li> <li>○ Identify issues</li> <li>○ Meet with delegated centre staff to review and resolve issues and DCFs in a report</li> <li>○ Record visit, outstanding issues and DCFs</li> <li>○ Retrain staff (centre &amp; SJM) conducting the investigation when necessary</li> </ul>
Close Out	<ul style="list-style-type: none"> <li>○ All patients enrolled at centre completed participation in the protocol</li> </ul>	<ul style="list-style-type: none"> <li>○ Review patient's consent</li> <li>○ Review patient data as compared to source document if necessary</li> <li>○ Generate DCFs for missing and/or inaccurate patient data recorded on the CRFs</li> <li>○ Review adherence with the protocol</li> </ul>	<ul style="list-style-type: none"> <li>○ Resolve outstanding issues from previous monitoring visits</li> <li>○ Review investigation site binder</li> <li>○ Identify issues</li> <li>○ Meet with delegated centre staff to review issues and DCFs</li> <li>○ Resolve all issues and DCFs</li> <li>○ Meet with investigator to discuss record retention and archiving; and final communication to the EC regarding the close of the investigation</li> <li>○ Record visit in a report</li> </ul>

#### 11.8.4 Designated monitors

Monitors are individuals, trained and qualified to ensure quality of the data and confirm adherence to the clinical investigational plan and clinical research agreement.

#### 11.8.5 Internal Quality Assessment

An investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized SJM employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

The purpose of the internal quality assessment is to determine whether the evaluated activities were appropriately conducted and the data were generated, recorded, analyzed and accurately reported according to the Clinical Investigational Plan, the signed Clinical Study Agreement, the Standard Operating Procedures (SOPs) and the applicable laws and regulations.

#### 11.8.6 Competent Authority (CA) Inspections

The investigator and/or designate should contact St. Jude Medical immediately upon notification of impending CA inspection. A clinical monitor will assist and immediately review investigational documentation with the investigator and/or designate to prepare for the audit.

An investigator who has authority to grant access shall permit authorized CA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where procedures are held (including any establishment where procedures are used or where records or results are kept).

An investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized CA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

An investigator shall permit authorized CA employees to inspect and copy records that identify patients, upon notice that CA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the sponsor or EC/IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

### **11.9 STUDY REPORT AND PUBLICATION POLICY**

After conclusion of the investigation, an integrated clinical and statistical report shall be written by the Sponsor in consultation with the clinical coordinating investigator.

The first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by the Sponsor. The Sponsor is entitled to delay publication in order to obtain patent protection. For more details regarding publications, refer to the publication Agreement.

## 11.10 SPONSOR CONTACTS

Contact	Telephone
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## **APPENDIX A: ABBREVIATIONS**

<b>Abbreviation</b>	<b>Description</b>
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFCL	Atrial Fibrillation Cycle Length
AHA	American Heart Association
AT	Atrial Tachycardia
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CCS SAF	Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale
CFE	Complex Fractionated Electrograms
CIP	Clinical Investigation Plan
CL	Cycle Length
CPL	Clinical Projects Leader
CRA	Clinical Research Associate
CS	Coronary Sinus
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form

Abbreviation	Description
ESC	European Society of Cardiology
ECG	Electrocardiogram
EGM	Intracardiac Electrograms
EQ-5D	EuroQol Group 5-Dimension
FU	Follow Up
GP	General Practitioner
HV	High Voltage
ICD	Implantable Cardioverter Defibrillator
INR	International Normalized Ratio
IFU	Instruction for Use
IRB	Institutional Review Board
ISB	Investigator Study Binder
LA	Left Atrium
MA	Mitral Anulus
MRI	Magnetic Resonance Imaging
PIC	Patient Informed Consent
PVA	Pulmonary Vein Antrum
PVI	Pulmonary Vein Isolation
PTCA	Percutaneous Coronary Angioplasty
RA	Right Atrium
SAE	Serious Adverse Event

Abbreviation	Description
SF 36	Short Form 36
SMF	Site Master File
SOP	Standard Operating Procedures
SJM	St. Jude Medical
TEE	Transesophageal echocardiogram
TTM	Trans Telephonic Monitor

## **APPENDIX B: REFERENCES**

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## **APPENDIX C: DECLARATION OF HELSINKI**

### **WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

#### **A. INTRODUCTION**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve

preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

## **B. PRINCIPLES FOR ALL MEDICAL RESEARCH**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information

about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified

individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

### **C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
  - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
  - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

## **APPENDIX D: LABELLING/ MANUALS**

The manuals for the EnSite NavX may be found on-line at [www.simplprofessional.com](http://www.simplprofessional.com) and should be consulted.

## **APPENDIX E: SYNOPSIS**

### **Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial – Part II. STAR AF II**

#### **Background**

To date, there is no randomized, multicenter trial addressing the best approach to AF ablation in persistent AF. It is unclear if PV antral isolation (PVI) is sufficient as alone strategy for persistent AF.

Furthermore, if additional substrate ablation is to be added, it is unclear if linear (PVI+Lines) or CFE ablation (PVI+CFE) should be the first choice approach. Thus, there is a good rationale for determining the best approach to AF ablation in patients with persistent AF.

#### **Hypothesis**

This investigation is designed with the hypothesis that combined PV Antral Isolation and Ablation of Complex Fractionated Electrograms (PVI+CFE) approach will offer a higher success rate compared to the Wide Circumferential Pulmonary Vein Antrum Isolation (PVI) approach and to the Combined PV Antral Isolation and Empiric Linear Ablation (PVI+Lines) approach.

#### **Inclusion / Exclusion Criteria**

##### **Inclusion Criteria**

- Patients age is 18 years or greater;
- Patients undergoing a first-time ablation procedure for AF;
- Patients with persistent AF - Persistent AF will be defined as a sustained episode lasting > 7 days and less than 3 years.
- Patients with symptomatic AF that is refractory to at least one antiarrhythmic medication - Symptomatic patients are those who have been aware of their AF at anytime within the last 5 years prior to enrollment. Symptoms may include, but are not restricted to, palpitations, shortness of breath, chest pain, fatigue, left ventricular dysfunction, or other symptoms, or any combination of the above.
- At least one episode of AF must have been documented by ECG, holter, loop recorder, telemetry, trans telephonic monitoring (TTM), or implantable device within last 2 years of randomization in this investigation;
- Patients must be able and willing to provide written informed consent to participate in this investigation; and
- Patients must be willing and able to comply with all peri-ablation and follow-up requirements.



Exclusion criteria:

- Patients with paroxysmal AF - Paroxysmal AF will be defined as a sustained episode lasting < 7 days.
- Patients with long-standing persistent AF - Long-standing persistent AF will be defined as a sustained episode lasting more than 3 years.
- Patients for whom cardioversion or sinus rhythm will never be attempted/pursued;
- Patients with AF felt to be secondary to an obvious reversible cause;
- Patients with contraindications to systemic anticoagulation with heparin or coumadin or a direct thrombin inhibitor;
- Patients with left atrial size  $\geq 60$  mm (2D echocardiography, parasternal long axis view); and
- Patients who are or may potentially be pregnant.

**Investigation Design**Type

This investigation is a prospective, randomized, parallel, single-blind and multicenter design.

Randomization

- Randomization is stratified by center.
- Patients will be randomized 1:4:4 into one of three arms:
  - Pulmonary vein antrum isolation (PVI) alone;
  - PVI plus ablation of complex fractionated electrograms (PVI+CFE); and
  - PVI plus empiric linear ablation (PVI+Lines).

**Endpoints**Primary Endpoint

- Freedom from documented AF episodes > 30 seconds at 18 months after one or two ablation procedure with/without antiarrhythmic medications.

Secondary Endpoints

- Freedom from documented atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Freedom from documented atrial flutter and atrial tachycardia episodes > 30 seconds at 18 months after one and two procedures with/without antiarrhythmic medications;
- Freedom from any atrial arrhythmia (documented or not) episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Freedom from symptomatic AF episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Freedom from symptomatic atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Incidence of peri-procedural complications, including stroke, PV stenosis, cardiac perforation, esophageal injury and death.
- Procedure duration;

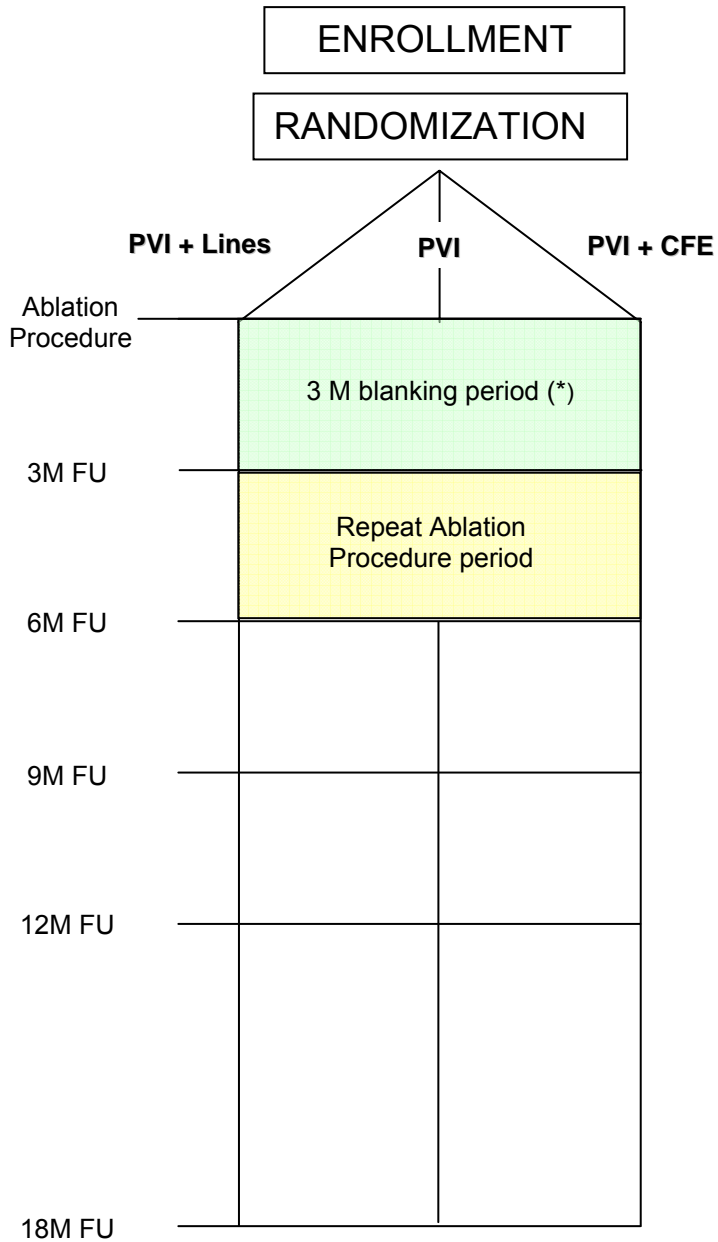
- Fluoroscopy time;
- Number of repeat procedures;
- Effect of each strategy on AF cycle length/regularity/termination;
- Relationship of acute termination of AF to long-term procedural outcome;
- Percentage achievement of complete linear block in linear ablation arm;
- Effect of complete linear block on procedural outcome in linear ablation arm;
- Quality of life measurements (SF-36, EQ-5D and CCS SAF) at baseline, 6, 12 and 18 months after one and/or two ablation procedures;
- Correlation of AF burden to symptoms and quality of life changes;
- Improvement in AF burden by > 90% post ablation procedure;
- Relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome;
- Cut off of AF burden that affects the Quality of Life measurement; and
- Evaluation of cost effectiveness.

### **Enrollment Target**

The enrollment target for this investigation is 549 patients.

The patient will participate in this investigation for 18 months from enrollment to the last follow-up.

**Project Flow**



(\*) During the 3 months blanking period the AF/AT/AFL recurrence will not be taken into account.

### **Follow-Up Procedures**

Follow Up visits will be performed according to Table 1 regardless of randomization group:

(\*) This is **only to be performed when applicable**.

	<b>When</b>	<b>Window</b>	<b>Activities</b>
Enrollment	Within 30 days before or during Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Eligibility</li> <li>• Patient Informed Consent</li> </ul>
Baseline Visit	Within 60 days before Ablation Procedure	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Demographics &amp; Physical Examination</li> <li>• Patient Cardiovascular History</li> <li>• Patient Current Cardiac Medications</li> <li>• Patient Medical History</li> <li>• Patient AF History</li> <li>• 12 Lead ECG Information</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
Ablation Procedure	Within 60 days after Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Randomization</li> <li>• Ablation Procedure Data Collection</li> <li>• Adverse Events(*)</li> </ul>
1st protocol follow-up	91 days after first Ablation Procedure (3 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events (*)</li> </ul>
Repeat Ablation Procedure	between day 91 – 183 (after first Ablation Procedure)	Not Applicable	<ul style="list-style-type: none"> <li>• Ablation Procedure Data collection</li> <li>• Adverse Events(*)</li> </ul>
2nd protocol follow-up	183 days after first Ablation Procedure (6 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
3rd protocol follow-up	274 days after first Ablation Procedure (9 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events(*)</li> </ul>

	When	Window	Activities
4th protocol follow-up	364 days after first Ablation Procedure (12 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
5th protocol follow-up	547 days post first Ablation Procedure (18 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>

## APPENDIX F: DATA COLLECTION

### CRF completion per visit

**X** It is **mandatory** to complete this CRF for this activity

**(X)** This is **only to be completed when applicable**.

	ENR	BASE	ABL	RE-ABL	FU	QoL	AE	DEV	DEATH	TERM
Enrollment	X						(X)	(X)	(X)	(X)
Baseline Visit		X				X	(X)	(X)	(X)	(X)
Ablation			X				(X)	(X)	(X)	(X)
Redo Ablation (within Blanking period)				X			X	X	(X)	(X)
3 M FU					X		(X)	(X)	(X)	(X)
Redo Ablation (between 3 – 6 Months)				X			X	(X)	(X)	(X)
6 M FU					X	X	(X)	(X)	(X)	(X)
Redo Ablation (after 6 Months)				X			X	X	(X)	(X)
9 M FU					X		(X)	(X)	(X)	(X)
12 M FU					X	X	(X)	(X)	(X)	(X)
18 M FU					X	X	(X)	(X)	(X)	(X)
Death							X		X	X

## **APPENDIX G: DATA COLLECTION METHOD**

Electronic data capture (EDC) will be used for this investigation, therefore please find below instructions on how to access and use the Electronic Case Report Form (eCRF) application.

Worksheets will be provided to assist in the collection of the data. The use of the worksheet is required.

### **Access to eCRF application**

The eCRF application is accessed through the internet and requires the use of a personal user name and password.

The following are required prior to receipt of Personal user name and password

- CV;
- Completed signature and delegation form;
- Documented Training; and
- Email address and telephone

Personal user name and password are provided by email. The first time the eCRF is accessed, the password will need to be changed.

If password is forgotten or lost, a new password will be provided by email by following the instructions on the webpage.

Each centre must be authorized to start enrolling patients in the investigation before access privileges to the eCRF application are made available.

Access privileges are based on the tasks assigned on the signature and delegation form and will be either:

- reviewing and data entry; or
- reviewing, data entry and signature

### **Worksheets**

Worksheets are provided to assist in collection of the data. When the worksheets are used, they need to be signed and dated and reside with the hospital records. If the worksheets are not used, hospital records must reflect and support all the information entered onto the eCRF.

# ST. JUDE MEDICAL™

## RDC OnSite Tip Card

- For protocol related questions please contact your FCE or project team.
- For any technical issues with RDC OnSite please call our toll free help line at 866-593-2910 or send an e-mail to [EDC@sim.com](mailto:EDC@sim.com).

### Logging Into RDC OnSite:

1. Click on the SJM Portal link provided to you by email. Enter your username and password. Pressing "Enter" will take you to the Study Site Portal. Click on the link to access the SJM Study Site Portal, where you can access information regarding your Study/Site.
2. Select the appropriate Study and Site Name from the dropdown menus. Pressing "Go" takes you to the Portal Study Home Page. **NOTE:** Applies to users with multiple SJM EDC studies. Users with access to a single EDC study are taken directly to the Portal Study Home Page upon entry.
3. Locate the 'EDC Data Entry' hyperlink on the left side. Clicking this hyperlink launches a new web browser opened to the RDC OnSite login screen.
4. Enter your Username and password again. You will be taken to the RDC OnSite Home Page where you can begin working with your study.

**NOTE:** Only one RDC OnSite session window can be open at a time. If you try to open additional sessions you will be logged out of any open sessions.

### Opening a Subject Casebook / Case Report Form (CRF):

1. From the RDC OnSite Home Page mark the checkbox under the "Select" column for each subject casebook to be viewed.
2. Select from the "Select Patients and..." dropdown menu field the "Open Patient Casebook" option and press "Go". You will be taken to the Casebook Page, where each selected subject casebook will be listed in table format.
3. From the Casebook Page click a CRF icon to open the CRF. A new web browser window will open known as the Data Entry Window (DEW).
4. If required, change the Study Visit by selecting it through the "Visit" dropdown menu.

### Routing Discrepancies to your FCRA / CRA – DEW Navigator Pane:

Route Discrepancies to your FCRA / CRA for resolution when:

- Data changes for Automated Edit Checks still violate Edit Check Rules; and
- Addressing manually entered Discrepancies.

1. Expand the Navigator Pane by clicking on the arrow on the right-edge of the DEW.
2. Click on an Active Discrepancy within the List sub-pane.
3. Review the Discrepancy Description within the Details sub-pane to assess the appropriate action. Change data on the CRF if required.
4. At the bottom of the Navigator Pane locate the "Action" dropdown menu field and select the "Send to CRA" option. Press "Go".
5. In the Discrepancy Action – Send to CRA dialogue window enter a Comment and press "OK" to route the Discrepancy to the FCRA / CRA.
6. After all CRF activities are completed save your changes by pressing the "Save" icon. Click the DEW Close icon "X" to return to the Casebook Page.

### Adding Scheduled and Unscheduled CRFs to a Study Visit – Casebook Page:

- **Add Visit Page** – Adds CRFs scheduled for the Study Visit (eg, another Implant form).
- **Add Other Page** – Adds CRFs not scheduled for the Study Visit (eg, an AE form to a 6-Month visit).

1. Mark the checkbox for the Subject casebook you want to add the CRF to and press either the "Add Visit Page" or "Add Other Page" button to open the appropriate dialogue window.
2. In the dialogue window select the radio button for the CRF to be added. Press the "Continue" button.
3. In the dialogue window the CRF sub-visit field will automatically be set to the next available number, therefore, you won't need to change it (for Add Visit Page only). Press the "Apply" button to continue. The CRF icon will appear in the Study Visit.
4. **If the CRF was added in error** and no data was saved onto the form, press the "Refresh" button and the CRF will be removed from the Study Visit.

**NOTE:** Add Visit Page can be used only after data entry is started on at least one scheduled CRF in that Study Visit.





**Summary of Casebook Status Icons – Home Page**

	No Data Entry is started.
	At least some Data Entry is saved. No Open Discrepancies.
	At least some Data Entry is saved. Active Discrepancy present on at least one CRF requiring current user's attention. May also include Other Discrepancies.
	At least some Data Entry is saved. Other Discrepancy present on at least one CRF requiring current user's attention. No Active Discrepancies present.

**Summary of CRF Status Icons – Casebook Page**

	CRF not started. Data entry is expected.
	Save Incomplete CRF – The CRF was started and only the Visit Header Date was completed.
	Save Incomplete CRF – Data Entry is incomplete. User is not done inputting all the data, and will finish at a later time.
	Save Complete CRF – Data Entry is complete. User has met all the requirements for the form, and the responses are considered complete. Automated Discrepancy Edit Checks are activated. CRF has no open issues.
	Save Complete CRF – Data Entry is complete. CRF contains Other Discrepancies that another user group must address.
	Save Complete CRF – Data Entry is complete. CRF contains Active Discrepancies that the current user group must address.
	*Approved CRF – CRF Data responses have been approved by an investigator. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	*CRF requires Re-Approval – Looped arrow next to signature indicates Data, an Investigator Comment, and/or Discrepancy was updated since the CRF was Approved. (If Open Discrepancies are present, the icon would also be red or yellow.)
	Verified CRF – CRF Data responses are verified against source documents. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Active Discrepancies present.
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Other Discrepancies present.
	*CRF is Verified and Approved – CRF Data responses are verified against source documents by the FCRA / CRA, and the Data responses approved by the Principal Investigator.
	CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Active Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Other Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF at Pass 2 Complete. This icon indicates Data Entry was completed by the sponsor in-house using data submitted on paper CRFs.

\*APPROVAL FEATURE CURRENTLY AVAILABLE TO INVESTIGATORS FOR THE DEATH CRF ONLY.

**Summary of Discrepancy Status Icons – Data Entry Window (DEW) Navigator Pane**

	Active Discrepancy that the current user group must address.
	Other Discrepancy that another user group must address.
	Resolved Discrepancy requiring no further action by any user group.

**NOTE:** Obsolete Discrepancies due to Data updates or Validation Procedure / Automated Edit Check updates will be removed from the List sub-pane.

**Summary of Data Entry Window (DEW) Toolbar Icons**

	Add Discrepancy		Delete Row		Approval History		*Print		First/Previous Page		Close
	Investigator Comment		Verification History		Approval		Save		Next/Last Page		

**DO NOT USE THESE TOOLBAR FUNCTIONS**

**Helpful Hints:**

- CRF Deletions** – If a CRF with saved data requires deletion notify your SJM contact, providing information about the form.
- Refresh** – Press the "Refresh" button to refresh RDC OnSite with current information (statuses, etc.)
- Printing a Subject Casebook / CRF** – Go to the RDC OnSite Report Page to print a Patient Data Report. Report types include casebooks with saved Subject data and blank Subject casebooks.
- Logout** – Use the web browser close icon "X" to exit. To re-enter, navigate through the SJM Portal.

## **APPENDIX H: RANDOMIZATION INSTRUCTIONS**

Before calling St. Jude Medical's (SJM) Automated Randomization System, you must have the following available:

1. Your 4-digit Authorization Code that will be provided by SJM
2. SJM Patient ID number.

You must call the SJM Automated Randomization System via a touch-tone telephone set, by calling the toll free number reported in the table below:

<b>Toll Free Numbers</b>	
<b>US and Canada</b>	<b>(800) 219-7285</b>
<b>Outside US or Canada</b>	<b>+1 (818) 493-2265</b>

To complete the randomization process, follow the instructions as you will hear by phone.

## **APPENDIX I: PATIENT INFORMATION SHEET AND PATIENT INFORMED CONSENT**

### **Patient Information Sheet Template**

#### **PATIENT INFORMATION SHEET**

### **Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial – Part II STAR AF II**

**<Name of the Investigator>**

**<Centre Address>**

**<Telephone Number>**

Dear Patient,

You are invited to take part in a research investigation. Before you decide on participating in this clinical trial, we would like to explain to you why we consider this research project is important and what it involves. Please take time to read the following information carefully and discuss it with your doctor. Ask your doctor if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The research is organized and funded by a medical company. This medical company is SJM international, Inc. The research is coordinated by:

St Jude Medical Coordination Centre  
The Corporate Village  
Building Figueras  
Da Vincilaan 11, Box F1  
1935 Zaventem  
Belgium

#### **What is the purpose of this investigation?**

The purpose of this research study is to collect information regarding the safety and efficacy of three different techniques used to treat atrial fibrillation. Atrial fibrillation is an abnormal heart rhythm in which the top chamber of your heart (the atrial chamber) beats very fast. The procedure performed to treat atrial fibrillation involves placing several catheters (long thin round solid tubes capable of conducting electricity to and from your heart) in your heart and heating the tip of one of these catheters to damage the tissues in particular regions of the atrium. These tissues are known to be responsible for your atrial fibrillation. This procedure is now being practiced at many hospitals and is not in itself experimental. Different techniques have been developed to eliminate atrial fibrillation by ablation. One technique targets tissues around the pulmonary veins (blood vessels that bring blood from the lung to the heart) where “triggers” for atrial fibrillation may be located. Another technique targets not only

targets the “triggers” described above, but also special areas around the atrium which are critical to causing atrial fibrillation to continue, characterized by certain signals (known as “complex fractionated electrograms” or “CFE”). A third technique targets the “triggers” as described above, but also modifies the atrium so that it cannot go into atrial fibrillation by creating lines of ablation in specific areas.

In all three techniques, a virtual positioning system similar to GPS (Global Positioning System) allows your doctor to track the position of the catheter(s) in your heart. All of the techniques have now been extensively studied individually, but they have never been compared against one another. The study will compare the occurrence of atrial fibrillation following ablation performed using either a trigger-based technique, a trigger-based technique plus CFE ablation, or a trigger-based technique plus ablation lines.

### **Conduct of the investigation**

A total of 549 patients will take part in this investigation which is expected to last approximately 3 years and is being conducted in up to 30 centers in Europe, Canada, Asia and Australia. Each patient will participate in the study for a period of 18 months.

If you decide to participate in this investigation, you will need to sign this document and you will be enrolled in the investigation.

Your physician has already determined that you need atrial fibrillation ablation. If you agree to participate in this study, you will be randomly (the same as flipping a coin) assigned to one of the three techniques used to achieve ablation of atrial fibrillation. You have a 1 out of 9 chance of having the trigger-based ablation procedure, a 4 out of 9 chance of having a trigger-based procedure plus CFE, and a 4 out of 9 chance of having a trigger-based procedure plus lines. You will then be followed by your physician/registered nurse at 3 months, 6 months, 9 months, 12 months, and 18 months.

Before the procedure, you will be asked to complete a Quality of Life questionnaire as well as have an echo test completed to measure heart function parameters.

The first follow up visit will be scheduled 3 months after the procedure. During this visit you will complete another questionnaire and be asked to wear a 24 hour heart monitor called a Holter monitor. The subsequent study visits will be the same, occurring at 6, 9, 12, and 18 months after the procedure.

You will also be asked to wear a special monitor that can transmit your heart rhythm over the telephone every time you press a button called a transtelephonic monitor (TTM). You will be asked to wear the TTM for the whole duration of the investigation. You will be asked to press the button on your TTM any time you feel any symptoms that you think may be atrial fibrillation. You will also be asked to press the button at least once a week when you are feeling well. This monitor is designed to be worn for long periods of time and you will be given information on how to put it on and take it off and how to operate it.

At the end of the study, you will continue to be followed in accordance with local practice.

### **Do I have to take part?**

Your participation in the investigation is completely voluntary, will not cost you anything and you will not be paid. If you decide to take part, you will be given this information sheet to keep and be asked to sign this form on the last page. If you

decide to take part, you are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

**What are the possible disadvantages and risks of taking part?**

The risks of atrial fibrillation ablation include: a small risk of bleeding or infection where the catheter enters the skin (less than 2%); a risk of perforating a hole in your heart which could require urgent drainage or urgent surgery (less than 2%); a risk of stroke (less than 1%); a risk of pulmonary vein stenosis, or narrowing of any one of the blood vessels that brings blood back to your heart causing permanent shortness of breath (less than 2%); and a risk of damaging the esophagus, or foodpipe, which lies right behind the heart (less than 0.1%). If the esophagus is damaged, a small connection can form between the heart and the esophagus, called a fistula, and this complication is almost always fatal (less than 0.1%).

There is no data suggesting that the risk of any of the above complications is any higher with one technique over the other.

There are no additional risks above and beyond undergoing atrial fibrillation ablation outside of the study if you choose to participate.

**What are the possible benefits of taking part?**

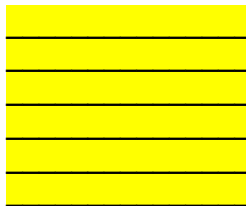
There may be no benefits to you for participating in this study. Medical science may benefit from your participation which may lead to benefits for future patients with this condition. Your participation may also contribute to the creation of new diagnostic tests, new medicines or other procedures that may have commercial value. However, your participation in this study will not entitle you to a share in any future economic benefits.

**What if new information becomes available?**

If significant new information is found during the study, you and your doctor will be given the information as soon as possible for review and discussion. The information could affect whether you continue to participate. If changes are made to the study or new findings develop during the course of the research, which may impact on your willingness to continue, you will be given relevant details and, if necessary, your consent will be requested again

**Will you be insured?**

The sponsor of this investigation concluded a special insurance for your participation: The insurance details are:



**Will my taking part in this investigation be kept confidential?**

If you consent to take part in the investigation, the information collected from your participation is considered as personal data. In order to check the data, it will be necessary to compare the data with your medical records. The sponsor, its representatives and sub-contractors, research team members and study monitors and regulatory agency staff may look at your study related medical records. All these people are obliged to observe strict confidentiality when handling the data or are bound by professional secrecy codes. Your name will **NOT** be disclosed outside the hospital.

Your personal data will be processed electronically to determine the outcome of the investigation. Your identity will be coded to preserve your anonymity. The data collected will be sent to the sponsoring company (in Belgium) for analysis.

Your data may be transferred to other countries where data privacy laws are less strict than those of European Union.

In accordance with the laws relating to data protection, you will be able to exercise your rights to access your personal data and to have any justifiable corrections made. If you wish to do so, you should request this from the doctor conducting the investigation.”

In participating in the investigation, you authorize the sponsoring company to use the information obtained during the investigation for scientific communications and publications.

If you agree, your General Practitioner will be informed of your participation in this investigation.

**What will happen to the results of the research investigation?**

The results will be analyzed for the purpose of publication in scientific journals without disclosing your identity.

**Contact for further information**

If you have any problems, concerns, questions or complaints about this investigation, you should preferably contact

Dr. \_\_\_\_\_ on \_\_\_\_\_.

Thank you for taking the time to think about taking part in this investigation.

If you agree to take part in this investigation, please complete and sign two of these documents on the last page together with your doctor. One signed document is for you, the other one will remain at this hospital.

This patient information consent form has been approved by

(enter EC name/details)

on

(enter date approved).

**Patient Information Consent Template**

**PATIENT INFORMED CONSENT (PIC)**

**Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial – Part II  
STAR AF II**

1. I understand that my participation is voluntary.
2. I understand that I am free to refuse to participate in the proposed investigation, without giving any reason and without my medical care or legal rights being affected.
3. I understand that I am free to withdraw from the proposed investigation at any time, without giving any reason, without my medical care or legal rights being affected.
4. I understand that anonymized data collected during the investigation prior to the withdrawal will be used in the analysis and communicated in publications.
5. I confirm that I have read and understand the information presented for the investigation and have had the opportunity to ask questions.
6. I agree to participate to the proposed investigation and to comply with the procedures related to it.
7. I give my permission to have my general doctor informed of my taking part in the investigation.
8. I give my permission that sections of any of my medical notes may be inspected by people from the company, company’s representatives, the ethics committee and regulatory authorities.

**2 copies of this consent form must be signed and dated by you and the investigator:**

**You will receive one copy of the Patient information sheet and the patient informed consent form and 1 copy is for the investigator to be filed in the investigator study binder.**

Name of patient	Signature	Date

Name of investigator consenting the patient	Signature	Date

## **APPENDIX L: CCS SAF SCALE**

The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale is determined by (S), symptoms attributable to AF; (A), association between symptoms (palpitations, dyspnea, dizziness/syncope, chest pain, weakness/fatigue) and documentation of AF or therapies for AF (ie, therapy associated symptoms); and (F), functional consequences of these symptoms on the patient’s daily function and quality of life.

The SAF class is then rated on a scale from 0 (asymptomatic) to 4 (severe impact of symptoms on QOL and activities of daily living). Table 1 shows how to determine the scale and Table 2 shows the scale definition.

Table 1: How to determine the CCS SAF Scale

<b>Step 1 - Symptoms</b>
<p>Identify the presence of the following symptoms:</p> <ul style="list-style-type: none"> <li>a. Palpitation</li> <li>b. Dyspnea</li> <li>c. Dizziness, presyncope or syncope</li> <li>d. Chest Pain</li> <li>e. Weakness or fatigue</li> </ul>
<b>Step 2 - Association</b>
<p>Is AF, when present, associated with the above-listed symptoms (a – e)?</p> <p>For example: Ascertain if any of the above symptoms are present during AF and likely caused by AF (as opposed to some other cause).</p>
<b>Step 3 - Functionality</b>
<p>Determine if the symptoms associated with AF (or the treatment of AF) affect the patient functionality (subjective quality of life)</p>



Table 2: CCS SAF Class Definition

Class 0
Asymptomatic with respect of AF
Class 1
<p>Symptoms attributable to AF have <b>minimal</b> effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Minimal and/or infrequent symptoms, or</li> <li>• Single episode of AF without syncope or heart failure</li> </ul>
Class 2
<p>Symptoms attributable to AF have a <b>minor</b> effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Mild awareness of symptoms in patients with persistent/permanent AF, or</li> <li>• Rare episodes (e.g. less than a few per year) in patients with paroxysmal or intermittent AF</li> </ul>
Class 3
<p>Symptoms attributable to AF have a moderate effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Moderate awareness of symptoms on most days in patients with persistent/permanent AF, or</li> <li>• More common episodes (e.g. more than every few months) or more severe Symptoms, or both, in patients with paroxysmal or intermittent AF.</li> </ul>
Class 4
<p>Symptoms attributable to AF have a severe effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Very unpleasant symptoms in patients with persistent/paroxysmal AF and/or</li> <li>• Frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF and/or</li> <li>• Syncope thought to be due to AF and/or</li> <li>• Congestive heart failure secondary to AF.</li> </ul>



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Project Name:	STAR AF II
Version:	3.0
Date:	2010 09 20

**SUBSTRATE AND TRIGGER ABLATION FOR  
REDUCTION  
OF ATRIAL FIBRILLATION TRIAL – PART II  
STAR AF II  
AF-09-102-ID-AB  
Clinical Investigational Plan (CIP)**

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## **2 AMENDMENT 1**

Based on decisions made by the Clinical Coordinating Investigator and after discussion with other Principle Investigators, the Clinical Investigational Plan has been modified as follows.

Amendment impact

	<b>Yes</b>	<b>No</b>
Change to Clinical Investigation Plan	X	
Change to Case Report Forms	X	
Change to Patient Information Sheet or Consent Form		X
Change to Required Procedures		X
Change to Synopsis		X

### Modification 1

Recommendation added to the protocol with regard to Echo Procedure performed pre ablation and post ablation.

#### Rational for Modification 1:

When Echo Procedures are performed, data on the structure of the heart should be documented in the case report form.

### Modification 2

Recommendation added to the protocol with regard to Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) performed pre ablation and post ablation.

#### Rational for Modification 1:

When CT scans or MRI are performed, data on the structure of the heart should be documented in the case report form.

### Modification 3

The term “cost effectiveness” in the secondary endpoint has been replaced with “cost utility”.

#### Rational for Modification 3:

The cost utility is the appropriate term for the analysis that will be done in the investigation.

### Modification 4

All Adverse Device Effects will be documented and reported to the sponsor and not only the Unexpected Adverse Device Effects.

#### Rational for Modification 4:

All Adverse Device Effects will be documented to be compliant with latest regulations and to SJM Standard Operative Procedures.

List of changes

Page & Paragraph(*)	CIP Version 1.0	CIP Version 2.0
Page 12 5.2.1.19	Evaluation Of Cost Effectiveness	Evaluation of Cost Utility
Page 24 10.2.3.2.1	All Serious Adverse Events and all Unexpected Adverse Device Effects are to be documented and reported to the sponsor immediately.	All Serious Adverse Events and all Adverse Device Effects are to be documented and reported to the sponsor immediately.
Page 32 10.7.2.2	<p>Patient Cardiovascular History</p> <ul style="list-style-type: none"> <li>• Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;</li> <li>• Provide the most recent value (within the last month) of the left ventricular ejection fraction (LVEF) derived from echocardiography or gated nuclear studies; and</li> <li>• Provide the most recent value of the left atrial size.</li> </ul>	<p>Patient Cardiovascular History</p> <ul style="list-style-type: none"> <li>• Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;</li> <li>• Provide the most recent value (within the last month) of the left ventricular ejection fraction (LVEF) derived from echocardiography or gated nuclear studies; and</li> <li>• Provide the most recent value of the left atrial size derived from echocardiography.</li> <li>• Provide the most recent degree of valvular heart disease derived from echocardiography.</li> </ul>
Page 33 10.8.1.2	Not Present	<p>Patients may undergo pre ablation CT Scan or MRI imaging of the left atrium as per site practice. If such imaging is performed, presence/absence of pre-existing PV stenosis should be reported in the Ablation Case Report Form.</p> <p>If CT Scan or MRI imaging is not performed, this will not be considered a protocol deviation.</p>
Page 33 10.8.1.3	Not Present	<p>Patients may undergo pre ablation transesophageal echocardiography as per site practice. If such imaging is performed, and a left atrial thrombus is detected, the ablation procedure should be deferred until thrombus is resolved.</p>

Page & Paragraph(*)	CIP Version 1.0	CIP Version 2.0
Page 44 10.8.9.3	Not Present	<p>Post-ablation CT/MRI imaging</p> <p>It is recommended, but not mandatory, that patients undergo CT or MRI imaging of the left atrium and of the Pulmonary Veins 3 to 6 months after the last ablation procedure to check for PV stenosis, especially if the patient has symptoms suggestive of PV stenosis.</p> <p>If CT Scan or MRI are performed, documentation of the degree of stenosis should be performed. Stenosis less than 50% will be graded as "mild," stenosis 50-69% will be graded as "moderate," and stenosis of 70% or more will be graded as "severe."</p>
Page 51 10.10.4	Not Present	<p>At the time of the last follow-up (18 months), it is recommended that patients have a final standard transthoracic echocardiogram to check left atrial size, valvular heart disease, and ejection fraction.</p> <p>If the transthoracic echocardiogram is performed, details of the echocardiographic data should be recorded on the final 18 month Follow Up Case Report Form.</p>

(\*) Page and paragraph refer to CIP Version 2.0.

### 3 AMENDEMENT 2

Based on decisions made by the Clinical Coordinating Investigator and after discussion with other Principle Investigators, the Clinical Investigational Plan has been modified as follows.

Amendment impact

	Yes	No
Change to Clinical Investigation Plan	X	
Change to Case Report Forms		X
Change to Patient Information Sheet or Consent Form		X
Change to Required Procedures		X
Change to Synopsis	X	

Modification 1

Mortality endpoint added as a secondary endpoint.

Rational for Modification 1:

Mortality endpoint added as requested by the Technische Universität München Ethics Committee.

Modification 2

Baseline activities can be performed within 60 days before the ablation procedure.

Rational for Modification 2:

Modification made to be consistent with what reported in Table 1 page 21.

Page & Paragraph(*)	CIP Version 2.0	CIP Version 3.0
Page 13 5.2.1.20	Not present	Mortality
Page 34 11.7.1	All Baseline activities are performed after patient is enrolled in the investigation and no more than 30 days prior to undergoing catheter ablation procedure.	All Baseline activities are performed after patient is enrolled in the investigation and no more than 60 days prior to undergoing catheter ablation procedure.
Page 80 Appendix E	Not present	Mortality

(\*) Page and paragraph refer to CIP Version 3.0



## 4 BACKGROUND

Atrial fibrillation (AF) is a very common arrhythmia affecting 1-2% of the American and Canadian population<sup>1</sup>. AF significantly impairs quality of life, increases the risk of stroke, and is associated with increased overall mortality<sup>2-5</sup>. Treatments to effectively eliminate AF and maintain sinus rhythm may not only improve patient quality of life, but may even reduce mortality<sup>6</sup>.

Recently, percutaneous catheter ablation has emerged as an effective, curative treatment for AF<sup>7-9</sup>. Initial techniques of ablation were developed based on the observation that AF was often triggered by frequent ectopic atrial activity emerging from the pulmonary veins<sup>7</sup>. By ablating these ectopic foci, AF initiation could be prevented in a substantial number of patients with paroxysmal AF<sup>7</sup>. In order to avoid the potential complication of pulmonary vein (PV) stenosis, and to improve success rates, the procedure has evolved<sup>10</sup>. While early procedures isolated the PVs at the level of the ostium, present-day procedures isolate outside of the tubular portion of the veins at the level of the funnel-shaped venous-atrial interface, sometimes referred to as the PV antrum (PVA)<sup>8,11,12</sup>. By isolating the PVAs from the atrium, ectopic activity from the PVs are no longer able to trigger AF. Single center experiences, and limited randomized trial data, have suggested reasonable success rates of PVA isolation for paroxysmal AF, ranging from 60-90% after one or two procedures<sup>9,11,12</sup>. In fact, the 2007 Heart Rhythm Society Consensus Statement on Catheter Ablation of AF states that PV isolation has become the “cornerstone” of present-day AF ablation<sup>22</sup>.

However, data on the efficacy of this so-called “trigger-based” strategy for more persistent AF populations is conflicting. First of all, the definition of “persistent” AF differs in the published literature, encompassing patients who have longer paroxysms of AF that are cardioverted early to patients who have permanent AF for years. Thus, the persistent AF population is not homogeneous and it should therefore not be surprising that success rates of a procedure would vary. Many reports have described reasonable success rates for PV isolation in mixed paroxysmal and persistent AF populations, but it is difficult to assess the success rates for each population separately from these studies. Others have suggested that PV isolation may achieve success rates in persistent AF comparable to paroxysmal AF after one or two procedures. More recent data, however, suggests that PV isolation achieves only moderate success in persistent AF, and that the success rates may be 15-40% lower than those quoted for paroxysmal AF<sup>14</sup>. Furthermore, the incidence of repeat ablation procedures with PV isolation alone may be higher in persistent AF. Thus, while trigger-based ablation is the most common technique for AF ablation, it may or may not be adequate for targeting higher burden AF populations.

In patients with persistent AF, it is believed that there may be additive benefit to targeting the atrial substrate responsible for AF maintenance in addition to the triggers for AF initiation. However, the best method to characterize and target this so-called “substrate” remains somewhat elusive. Creation of linear lesions across critical structures of the left and/or right atrium has been used for this purpose. From the early surgical experiences with the Maze and modified Maze procedures, creation of

complete linear lesions may be very effective in preventing the development of AF. One mechanism by which this may work is division of the atrium into isolated segments that are too small to sustain the multiple wavelets required to perpetuate AF. Another mechanism may be that linear lesions prevent development of macro-reentrant atrial flutters/tachycardias which are a frequent cause of recurrence post-catheter ablation of AF. Finally, linear lesions may transect structures that harbor key rotors for AF maintenance, such as the posterior wall, the PV antral border, the roof, and the septum. Single-center studies have suggested that addition of linear lesions to PV isolation may improve procedural efficacy for both paroxysmal and persistent AF. Others have suggested that addition of linear lesions is essential for prevention of iatrogenic flutters/tachycardias. Another study showed that addition of linear lesions may have equivalent or better efficacy to ablation of other adjuvant targets such as complex fractionated electrograms. The data is not all consistent, however, with some data showing that linear ablation may not add much to PV isolation. Furthermore, creation of linear lesions with documentation of conduction block can be time-consuming and hard to demonstrate, particularly along the mitral annulus and the septum. Creation of linear lesions without complete block may also be proarrhythmic.

Complex fractionated electrograms (CFE) may represent another target for the substrate for AF maintenance. CFE are very rapid or continuously fractionated electrograms that may represent key “rotor” or “pivot points” where wavelets can turn around and create opportunities for reentry that maintain AF<sup>15,16,17</sup>. One study suggested that targeting CFE alone, without PV isolation, can eliminate AF with high success rates in excess of 70%<sup>24</sup>. However, this result has not been duplicated by other investigators. Instead, CFE may be a useful adjuvant target to PV isolation, increasing success rates over trigger-based ablation alone. In the pilot STAR-AF trial (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation)<sup>23</sup>, we found that CFE alone was not an effective approach for AF ablation in high-burden paroxysmal and persistent patients. However, when CFE was combined with PV isolation, the strategy was more effective than either approach alone, with some suggestion of greater effectiveness in those with persistent AF. The patient numbers for this subgroup analysis were quite small, however, so the data was not conclusive. Furthermore, while some studies have supported the addition of CFE ablation for persistent AF, others have not. One of the greatest problems is in the subjectivity in identifying CFE. With the use of automated CFE mapping algorithms, localization of CFE may be more objective and consistent, with better results compared to visual identification alone. CFE regions may also demonstrate greater temporal and spatial stability when electrograms are analyzed over a short period of time, as happens with automated algorithms.

Data from a monocenter study suggested the combination of PV isolation with linear ablation and targeting of CFE<sup>25</sup>. While this procedure may reach the highest success rates, it is a very time-consuming process. Often, these procedures are over 6-8 hours in duration and often require two or more visits to the electrophysiology lab. Furthermore, many of the patients in the report remained on antiarrhythmic medications, so it is unclear what the additive benefit of such an extensive procedure is in comparison to linear or CFE adjuvant ablation alone.

To date, there is no randomized, multicenter trial addressing the best approach to AF ablation in persistent AF. However, this particular group of patients represents the

fastest rising group being ablated in most centers, and the majority of AF patients in the population. It is unclear if PV antral isolation (PVI) is sufficient as a lone strategy for persistent AF. Furthermore, if additional substrate ablation is to be added, it is unclear if linear (PVI+Lines) or CFE ablation (PVI+CFE) should be the approach of first choice. Thus, there is a good rationale for determining the best approach to AF ablation – trigger or combined trigger and substrate – in patients with persistent AF.

## **5 OBJECTIVES**

### **5.1 PRIMARY OBJECTIVES**

5.1.1 The primary objective of this investigation is to compare the efficacy of three different AF ablation strategies in patients with persistent AF targeting:

- 5.1.1.1 Only the triggers of AF via PV antrum isolation (PVI) alone;
- 5.1.1.2 A combination of the triggers plus the substrate of AF as defined by complex fractionated electrograms (PVI+CFE); and
- 5.1.1.3 A combination of the triggers plus the substrate of AF by empiric linear ablation (PVI+Lines).

### **5.2 SECONDARY OBJECTIVES**

5.2.1 The secondary objectives of this investigation are to evaluate and compare:

5.2.1.1 The safety and procedural characteristics of:

- PVI alone versus
- PVI+CFE versus
- PVI+Lines.

5.2.1.2 The quality of life between patients treated with:

- PVI alone versus
- PVI+CFE versus
- PVI+Lines.

## **6 ENDPOINTS**

### **6.1 PRIMARY ENDPOINT**

- 6.1.1 Freedom from documented AF episodes > 30 seconds at 18 months after one or two ablation procedure with/without antiarrhythmic medications.

### **6.2 SECONDARY ENDPOINTS**

- 6.2.1 The secondary endpoints of this investigation are:
  - 6.2.1.1 Freedom from documented atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 6.2.1.2 Freedom from documented atrial flutter and atrial tachycardia episodes > 30 seconds at 18 months after one and two procedures with/without antiarrhythmic medications;
  - 6.2.1.3 Freedom from any atrial arrhythmia (documented or not) episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 6.2.1.4 Freedom from symptomatic AF episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 6.2.1.5 Freedom from symptomatic atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
  - 6.2.1.6 Incidence of peri-procedural complications, including stroke, PV stenosis, cardiac perforation, esophageal injury and death.
  - 6.2.1.7 Procedure duration;
  - 6.2.1.8 Fluoroscopy time;
  - 6.2.1.9 Number of repeat procedures;
  - 6.2.1.10 Effect of each strategy on AF cycle length/regularity/termination;
  - 6.2.1.11 Relationship of acute termination of AF to long-term procedural outcome;
  - 6.2.1.12 Percentage achievement of complete linear block in linear ablation arm;
  - 6.2.1.13 Effect of complete linear block on procedural outcome in linear ablation arm;
  - 6.2.1.14 Quality of life measurements (SF-36, EQ-5D and CCS SAF) at baseline, 6, 12 and 18 months after one and/or two ablation procedures;
  - 6.2.1.15 Correlation of AF burden to symptoms and quality of life changes;
  - 6.2.1.16 Improvement in AF burden by > 90% post ablation procedure;

- 6.2.1.17 Relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome;
- 6.2.1.18 Cut off of AF burden that affects the Quality of Life measurement;
- 6.2.1.19 Evaluation of cost utility; and
- 6.2.1.20 Mortality.

## **7 PATIENT SELECTION CRITERIA**

### **7.1 PATIENTS ENROLLMENT**

A patient who meets all the inclusion criteria and does not meet any of the exclusion criteria is eligible to participate in the investigation. A patient is enrolled in the investigation only when s/he has provided written informed consent. Once enrolled, a patient is expected to comply with the scheduled visits and required activities according to the protocol.

### **7.2 INCLUSION CRITERIA**

- 7.2.1 Patients age is 18 years or greater;
- 7.2.2 Patients undergoing a first-time ablation procedure for AF;
- 7.2.3 Patients with persistent AF;
  - 7.2.3.1 Persistent AF will be defined as a sustained episode lasting > 7 days and less than 3 years.
- 7.2.4 Patients with symptomatic AF that is refractory to at least one antiarrhythmic medication;
  - 7.2.4.1 Symptomatic patients are those who have been aware of their AF at anytime within the last 5 years prior to enrollment. Symptoms may include, but are not restricted to, palpitations, shortness of breath, chest pain, fatigue, left ventricular dysfunction, or other symptoms, or any combination of the above.
- 7.2.5 At least one episode of persistent AF must have been documented by ECG, holter, loop recorder, telemetry, trans telephonic monitoring (TTM), or implantable device within last 2 years of enrollment in this investigation;
- 7.2.6 Patients must be able and willing to provide written informed consent to participate in this investigation; and
- 7.2.7 Patients must be willing and able to comply with all peri-ablation and follow-up requirements.

## 7.3 EXCLUSION CRITERIA

- 7.3.1 Patients with paroxysmal AF;
  - 7.3.1.1 Paroxysmal AF will be defined as a sustained episode lasting < 7 days.
- 7.3.2 Patients with long-standing persistent AF;
  - 7.3.2.1 Long-standing persistent AF will be defined as a sustained episode lasting more than 3 years.
- 7.3.3 Patients for whom cardioversion or sinus rhythm will never be attempted/pursued;
- 7.3.4 Patients with AF felt to be secondary to an obvious reversible cause;
- 7.3.5 Patients with contraindications to systemic anticoagulation with heparin or coumadin or a direct thrombin inhibitor;
- 7.3.6 Patients with left atrial size  $\geq 60$  mm (2D echocardiography, parasternal long axis view); and
- 7.3.7 Patients who are pregnant.
  - 7.3.7.1 Pregnancy will be assessed by patients informing the physicians.



## **8 INVESTIGATION DESIGN**

### **8.1 TYPE**

- 8.1.1 This investigation is a randomized, prospective, parallel, single-blind multicenter design.

### **8.2 DURATION**

- 8.2.1 The first enrollment is anticipated in Q3 2010.
- 8.2.2 The enrollment period will be approximately 18 months.
- 8.2.3 The patient will participate in this investigation for approximately 18 months from enrollment to the last follow-up.
- 8.2.4 The patient may withdraw from the investigation at any time, for any reason. In this case, the procedures for reporting should be followed as mentioned in the section 11.4 Early Conclusion to Patient Participation.

### **8.3 ENROLLMENT TARGET**

- 8.3.1 The enrollment target for this investigation is 549 patients. For more information, refer to section 10.1 Sample Size Justification.

### **8.4 RANDOMIZATION**

#### **8.4.1 Randomization Stratifications**

- 8.4.1.1 Randomization is stratified by center.

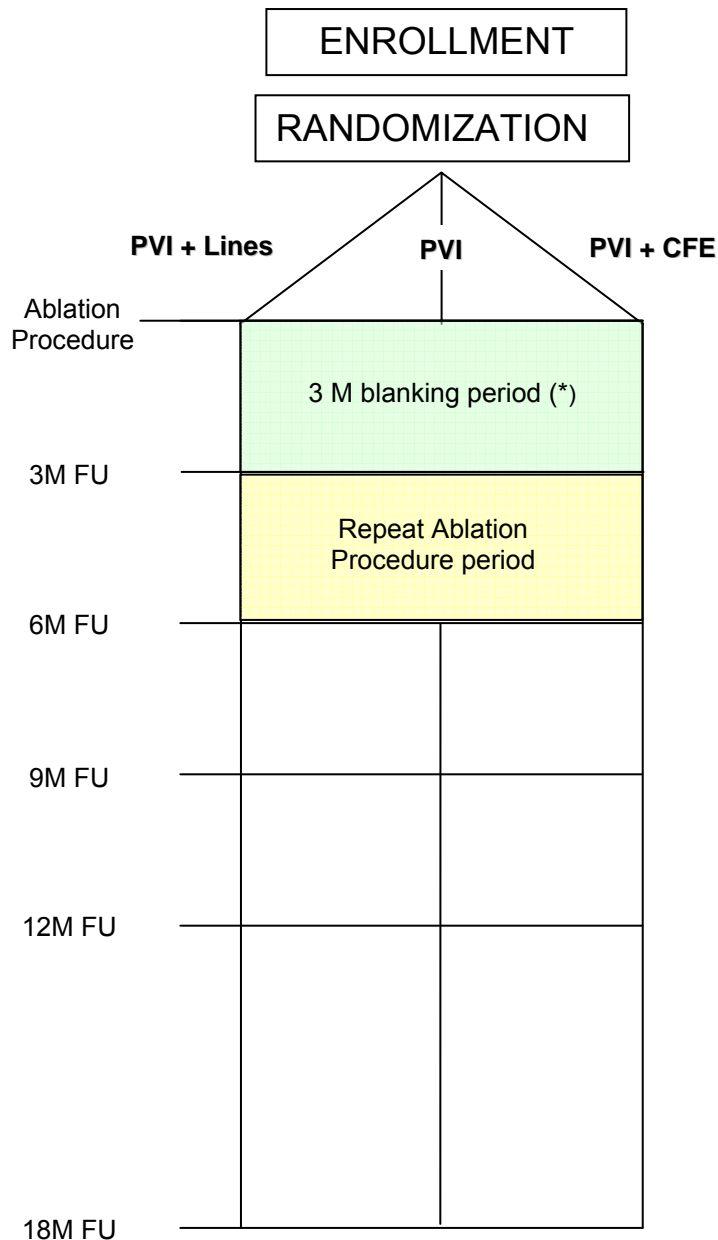
#### **8.4.2 Randomization Arms**

- 8.4.2.1 Patients are randomized in a 1:4:4 fashion to one of the investigation arms:

- Pulmonary vein antrum isolation alone (**PVI**);
- Pulmonary vein antrum isolation plus ablation of complex fractionated electrograms (**PVI+CFE**);
- PVI plus empiric linear ablation (**PVI+Lines**).

8.4.2.2 Because of the nature of the ablation procedures, physicians cannot be blinded to the randomization. Patients will be blinded to their ablation strategy (single-blind design).

## 8.5 DESIGN



(\*) AF/AT/AFL recurrence during the blanking period will not be taken into account.

## **9 PRODUCT**

### **9.1 PRODUCTS**

The following market approved St. Jude Medical products are required to be used in the investigation:

- 9.1.1 Cardiac Mapping System - Ensite NavX System; and
- 9.1.2 EnSite Complex Fractionated Electrograms Algorithm – CFE.

NOTE: The protocol will be opened to any new commercially available products.

### **9.2 ADDITIONAL PRODUCTS**

The following market approved products are required to be used in the investigation regardless of the manufacturer:

- 9.2.1 Open irrigated tip ablation catheter;
- 9.2.2 Radiofrequency (RF) ablation system;
- 9.2.3 Coronary sinus electrophysiology catheter (minimum 4 electrodes); and
- 9.2.4 Circular mapping catheter (minimum 10 electrodes).

The following market approved products are recommended to be used in the investigation regardless of the manufacturer:

- 9.2.5 Steerable and fixed introducers.

## **10 SCIENTIFIC SOUNDNESS**

### **10.1 SAMPLE SIZE JUSTIFICATION**

- 10.1.1 The sample size calculation is based on the hypothesis and study design. It is expected that the survival proportion (Freedom from AF) in PVI+CFE group is 75%, the survival proportion (Freedom from AF) in PVI+Lines group is 60% and the survival proportion (Freedom from AF) in PVI group is 45%. A one-sided log rank test was used for sample size calculation.
- 10.1.2 In order to test if the PVI+CFE strategy is superior to the PVI+Lines strategy and PVI strategy, a total of 468 patients is needed to maintain a overall power of 90% at a significance level of 5%, and with randomization ratio of 1:4:4 (PVI: PVI+CFE: PVI+Lines), 52 patients in PVI group, 208 each in PVI+CFE group and PVI+Lines group are needed.
- 10.1.3 Taking into account the drop out of 15%, a total of 549 patients (61 in PVI group, 244 each in PVI+CFE group and PVI+Lines group) will be recruited.

### **10.2 HYPOTHESES**

- 10.2.1 The combined trigger and substrate approaches (PVI+CFE) will be superior to the triggers and linear ablation approach (PVI + Lines) and trigger-based strategy alone (PVI) in terms of freedom from AF at 18 months after one or two ablation procedure.

$$10.2.1.1 \quad H_0 : S_{COM} \leq S_{Line} \quad vs \quad H_1 : S_{COM} > S_{Line}$$

$$10.2.1.2 \quad H_0 : S_{COM} \leq S_{PVI} \quad vs \quad H_1 : S_{COM} > S_{PVI}$$

- 10.2.2 Where  $S_{COM}$  is the survival proportion (Freedom from AF) at 18 month after one or two ablations in PVI+CFE group;  $S_{Line}$  is the survival proportion (Freedom from AF) at 18 month after one or two ablations in PVI+Lines group;  $S_{PVI}$  is the survival proportion (Freedom from AF) at 18 month after one or two ablations in PVI group.

### **10.3 PRIMARY ENDPOINT ANALYSIS**

- 10.3.1 The primary endpoint analyses will be based on the intention-to-treat (ITT) principle comparing treatment randomized and all protocol deviators will be included. Secondary per-protocol (PP) analyses will compare patient data based on the actual treatment received and will exclude protocol deviators.
- 10.3.2 The log rank test will be used for the hypothesis and a p value of less than 0.05 will be considered to indicate statistical significance. Besides, the length of time to the recurrence of AF in each group was compared visually by the Kaplan–Meier curves.
- 10.3.3 Any baseline demographic factor, which is found to be significantly different between the treatments, will be assessed its impact on the primary endpoint analysis. For this purpose, a Cox regression model with treatment and above baseline factor will be used.

### **10.4 SECONDARY ENDPOINT ANALYSIS**

- 10.4.1 All time to event endpoints will be analyzed using log rank tests. Results will be expressed in terms of median survival times per group, hazard ratios, and p-values.
- 10.4.2 For quality of life, a linear mixed model will be used to test the association between quality of life score and the factors including treatment, AF burden and time. Results will be expressed in terms of p-values.
- 10.4.3 The continuous variables will be summarized using descriptive statistics (mean, standard deviation, median, range) and comparisons between the randomization groups will be performed using ANOVA, and equivalent non-parametric method, Kruskal-Wallis test, will be used in case the assumption for ANOVA is violated. Normality of data will be checked with the aid of box plots, normal quartile plots, and normality tests. Results will be expressed in terms of p-values.
- 10.4.4 All categorical data will be presented using frequencies and percentages, and the comparisons between the randomization groups will be performed using chi-square tests if each cell in the contingency table has an expected frequency of five or more. If this is violated, Fisher's exact test will be used instead. Results will be expressed in terms of p-values.

## 11 PROTOCOL DESCRIPTION

### 11.1 PROTOCOL PROCEDURES - OVERVIEW

Table 1 – Protocol Procedure Overview

These activities are applicable to all patients regardless of randomization group.  
 (\*) This is **only to be performed when applicable**.

	When	Window	Activities
Enrollment	Within 30 days before or during Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Eligibility</li> <li>• Patient Informed Consent</li> </ul>
Baseline Visit	Within 60 days before Ablation Procedure	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Demographics &amp; Physical Examination</li> <li>• Patient Cardiovascular History</li> <li>• Patient Current Cardiac Medications</li> <li>• Patient Medical History</li> <li>• Patient AF History</li> <li>• 12 Lead ECG Information</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
Ablation Procedure	Within 60 days after Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Randomization</li> <li>• Ablation Procedure Data Collection</li> <li>• Adverse Events(*)</li> </ul>
1 <sup>st</sup> protocol follow-up	91 days after first Ablation Procedure (3 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events (*)</li> </ul>
Repeat Ablation Procedure	between day 91 – 183 (after first Ablation Procedure)	Not Applicable	<ul style="list-style-type: none"> <li>• Ablation Procedure Data collection</li> <li>• Adverse Events(*)</li> </ul>
2nd protocol follow-up	183 days after first Ablation Procedure (6 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
3rd protocol follow-up	274 days after first Ablation Procedure (9 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events(*)</li> </ul>

	When	Window	Activities
4th protocol follow-up	364 days after first Ablation Procedure (12 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
5th protocol follow-up	547 days post first Ablation Procedure (18 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>

## 11.2 ADVERSE EVENTS

### 11.2.1 Definition of Adverse Event, Adverse Device Effect, Serious Adverse Event and Serious Adverse Device effect according to ISO 14155:

11.2.1.1 **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation patient.

11.2.1.1.1 This definition does not necessarily imply that there is a causal relationship between the adverse event and the device under investigation.

11.2.1.2 **Adverse Device Effect (ADE)** is defined as any untoward and unintended response to a medical device.

11.2.1.2.1 This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. It also includes any event that is a result of a user error.

11.2.1.3 **Serious Adverse Event (SAE)** is defined as an adverse event that:

11.2.1.3.1 Led to death;

11.2.1.3.2 Led to a serious deterioration in the health of a patient that:

- Resulted in a life threatening illness or injury;
- Resulted in a permanent impairment of a body structure or a body function;
- Required in-patient hospitalization or prolongation of existing hospitalization; and
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

11.2.1.3.3 Led to foetal distress, foetal death or a congenital abnormality or birth defect.

11.2.1.4 **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.



### 11.2.2 List of Anticipated Adverse Events and Adverse Device Effects:

11.2.2.1 The following represents a list of anticipated Adverse Events (AE) and Adverse Device Effects (ADE) experienced in either animal and/or clinical studies to date with AF ablation procedures, or reported in instructions for use and literature. Possible Adverse Events (AE) and Adverse Device Effects (ADE) include but are not limited to the following:

Table 2 –Possible Adverse Events and Adverse Device Effects

Cardiac Events	Non-cardiac Events
<ul style="list-style-type: none"> <li>• Abnormal ECG</li> <li>• Angina (chest pain)</li> <li>• Arrhythmia</li> <li>• AV fistula</li> <li>• Complete heart block</li> <li>• Coronary artery injury</li> <li>• Cardiac Perforation</li> <li>• Cardiac Thromboembolism</li> <li>• CHF exacerbation – fluid overload</li> <li>• Component damage to ICD or implantable pacemaker</li> <li>• Death</li> <li>• Dislodgement of implantable cardioverter defibrillator or permanent pacing lead.</li> <li>• Endocarditis</li> <li>• Exacerbation of pre-existing atrial fibrillation</li> <li>• Heart Failure</li> <li>• Hypotension</li> <li>• Inadvertent AV block (complete heart block)</li> <li>• Left atrial / esophageal fistula</li> <li>• Myocardial infarction</li> <li>• Obstruction/perforation/damage of the vascular system</li> <li>• Palpitation</li> <li>• Pericardial effusion/cardiac tamponade</li> <li>• Pericardial effusion without tamponade</li> <li>• Pericarditis</li> <li>• Pulmonary vein dissection</li> <li>• Pulmonary vein stenosis</li> <li>• Pulmonary vein thrombus</li> <li>• Temporary or complete heart block</li> <li>• Unintended (in)complete AV, sinus node, heart block/damage</li> <li>• Vessel wall/valvular damage or insufficiency</li> <li>• Ventricular arrhythmia requiring defibrillation</li> </ul>	<ul style="list-style-type: none"> <li>• Air embolism</li> <li>• Anesthesia reaction</li> <li>• Cerebrovascular accident</li> <li>• High creatinine phosphokinase (CPK)</li> <li>• Infections</li> <li>• Local hematomas / ecchymosis</li> <li>• Laceration</li> <li>• Phrenic nerve damage</li> <li>• Pneumonia</li> <li>• Pneumothorax</li> <li>• Pulmonary edema</li> <li>• Pulmonary embolism</li> <li>• Pulmonary hypertension</li> <li>• Pleural effusion</li> <li>• Pseudoaneurysm</li> <li>• Respiratory depression</li> <li>• Skin burns</li> <li>• Syncope</li> <li>• Transient ischemic attack</li> <li>• Vasovagal reactions</li> </ul>

### 11.2.3 Procedure for Recording and Reporting Adverse Events

11.2.3.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation, regardless of the randomization group.

11.2.3.2 Safety surveillance and reporting starts at the time when the patient is enrolled into the investigation (date of signature of the informed consent) until the last investigational visit has been performed, or the patient has died, or the patient concludes his participation into the study.

11.2.3.2.1 **All Serious Adverse Events** and **all Adverse Device Effects** are to be documented and reported to the sponsor **immediately**.

11.2.3.2.2 **Non-Serious Adverse Events** documentation and reporting are limited to cardiovascular and neurovascular events. Within cardiovascular, all arrhythmias that require medical assessment and/or intervention should be documented as an adverse event.

11.2.3.3 Should an AE occur, record AE information in the hospital records, document the information into the Adverse Event case report form (CRF) as soon as possible. By completing the CRF the sponsor will be notified.

11.2.3.3.1 Refer to appendices “Data Collection” and “Data Collection Method”.

11.2.3.3.2 Access the eCRF application.

11.2.3.3.3 Select the visit the AE is related to or indicate it as unscheduled visit.

11.2.3.3.4 Enter adverse event information into the **AE Notification** section of the CRF.

- Date the AE occurred;
- Date the center investigator or delegate became aware of the AE;
- Main complaints/symptoms of the AE;
- Initial diagnosis of the AE;
- Potential cause of the AE;
- Pre-existing medical conditions related to the AE;
- Seriousness of the AE;
- Device relationship to AE; and
- Status of the AE.

11.2.3.3.5 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

11.2.3.3.6 The CRF must be authorized by the principal investigator or delegated co-investigator.

11.2.3.3.7 As soon as the final details are available for the adverse event, the information should be reported on the AE Follow-Up section of the CRF.

11.2.3.3.8 Access the eCRF application.

11.2.3.3.9 Edit AE CRF, document information into the **AE Follow-Up** section of the case report form.

- Hospitalization details (if applicable);
- Diagnostic test information (if applicable);
- Treatment given (if applicable);
- Final medical diagnosis & cause;
- Patient condition;
- Final AE status;
- Seriousness of AE based on final medical diagnosis and cause;
- Relationship of AE to device based on final medical diagnosis & cause.

11.2.3.3.10 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

11.2.3.3.11 The CRF must be authorized by the principal investigator or delegated co-investigator.

11.2.3.4 Additional information will be requested, if necessary, by the Sponsor for reporting of AEs to regulatory authorities.

11.2.3.5 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

**NOTE:** If an adverse event is documented at the patient's last follow up visit (18 months), both the notification and follow-up information on the AE CRF are to be provided to the sponsor.

Pre-existing cardiac conditions that require planned hospitalization are not to be considered as AE.

## 11.3 PATIENT DEATH

### 11.3.1 Procedure for Recording and Reporting Patient Death

11.3.1.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation, regardless of the randomization group.

11.3.1.2 Safety surveillance and reporting starts at the time when the patient is enrolled into the investigation (date of signature of the informed consent) until the last investigational visit has been performed.

11.3.1.2.1 All **Patient Deaths** are to be documented and reported to the sponsor **immediately**.

11.3.1.3 Should death occur, record death information in the hospital records, **immediately** document the information in the Death case report form (CRF). By completing the CRF the sponsor will be notified.

11.3.1.3.1 Refer to appendices “Data Collection” and “Data Collection Method”.

11.3.1.3.2 Access the eCRF application.

11.3.1.3.3 Select the visit the patient death is related to or indicate it as visit unscheduled visit.

11.3.1.3.4 Enter patient death information into the Patient Death CRF.

- Date the death occurred;
- Date the center investigator or delegate became aware of the death;
- Place where death occurred (e.g. hospital, nursing home, patient’s home);
- If death was witnessed;
- If autopsy was performed;
- Temporal cause of death
- Primary cause of death;
- Details regarding death; and
- If details of serious adverse event associated to the death are known by the center/investigator/delegate.

11.3.1.3.5 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

11.3.1.3.6 The CRF must be authorized by the principal investigator or delegated co-investigator.

11.3.1.4 Patient death may be an outcome of a serious adverse event (SAE).

11.3.1.4.1 If the death is related to a SAE, all the efforts to get SAE details should be made and the Adverse Event CRF must be completed.

11.3.1.5 Patient death is an early conclusion to the patient's participation in the investigation. Complete Termination CRF.

11.3.1.6 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

## 11.4 EARLY CONCLUSION TO PATIENT PARTICIPATION

- 11.4.1 All reasonable efforts should be made to retain the patient in the clinical investigation until completion of the clinical investigation.
- 11.4.2 If a patient concludes their participation in the investigation, the patient's future management will not be changed by this decision, whether it is voluntary or otherwise,
- 11.4.2.1 A patient/family member may request to withdraw from the investigation at any time; She/he would be able to do so without having to justify it and without affecting her/his relationship with the investigator.
- 11.4.2.2 A patient dies. Refer to section 11.3, "Patient Death"; or
- 11.4.2.3 An investigator may withdraw a patient from the investigation at any time if she/he thinks it is in the patient's best interest; or
- 11.4.2.4 A investigator may withdraw a patient, if the patient does not come for their scheduled visits and/or is not compliant with the regimen of the protocol. This patient will be considered "lost to follow-up"; A patient will be considered "lost to follow-up" when 3 attempts to contact the patient were unsuccessful: A minimum of 2 documented phone calls by a physician/delegate to the patient/emergency contact and a certified letter sent to the last known address.
- 11.4.2.5 The Investigation is temporarily stopped or terminated, either at the local, national or international level, at the request of Ethics Committees, Competent Authorities, Departments of Health or the investigation Sponsor.
- 11.4.3 Should a patient withdraw and conclude participation in the investigation, document the information in the Termination case report form (CRF) as soon as possible. By completing the CRF the sponsor will be notified.
- 11.4.3.1 Refer to appendices "Data Collection" and "Data Collection Method".
- 11.4.3.2 Access the eCRF application.
- 11.4.3.3 Select the visit the patient death is related to or indicate it as visit unscheduled visit.
- 11.4.3.4 Enter patient early conclusion information into the Termination CRF.
- Date the early conclusion occurred; and
  - Reason for the early conclusion;
- 11.4.4 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.
- 11.4.5 The CRF must be authorized by the principal investigator or delegated co-investigator.

## 11.5 DEVIATIONS

- 11.5.1 Investigators are required to adhere to the Investigational Plan, signed Investigator's Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate Ethics Committees or applicable regulatory authorities.
- 11.5.2 A **Deviation** is defined as a situation in which there is a non-compliance with the protocol.
- 11.5.3 Anticipated deviations:
- 11.5.3.1 Patient Informed Consent is not approved by Ethics Committee;
  - 11.5.3.2 Patient Informed Consent is not sign and/or date by the patient and/or investigator;
  - 11.5.3.3 Study specific procedure was performed before the Patient Informed Consent was signed and dated by patient;
  - 11.5.3.4 Investigational Required Visit not performed;
  - 11.5.3.5 Investigational Required Visit performed outside the window;
  - 11.5.3.6 24 hour Holter not performed/ data corrupted and not available;
  - 11.5.3.7 ECG not performed/ data corrupted and not available;
  - 11.5.3.8 Patient crossover from assigned randomization group; and
  - 11.5.3.9 Repeat ablation performed out of the repeat ablation window (3 – 6 months).
- 11.5.4 Should a deviation occur, document the information in the Deviation case report form (CRF). By completing the CRF the sponsor will be notified.

**NOTE:** When a deviation occurs after enrollment for **patient consent**, record the information in the hospital record, **immediately** document the information in the Deviation and Termination case report form (CRF). By completing the CRF the sponsor will be notified.

Refer to appendices "Data Collection" and "Data Collection Method".

Access the eCRF application.

Select the scheduled or unscheduled visit the deviation is related to.

Enter deviation information into the Termination CRF.

- Date of deviation
- When the deviation occurred
- Type of deviation
- Medical justification

Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

The CRF must be authorized by the principal investigator or delegated co-investigator.

When a deviation occurs after enrollment for **patient eligibility**, record the information in the hospital record, **immediately** document the information in the Deviation case report form (CRF). By completing the CRF the sponsor will be notified. All the efforts should be made to keep the patient in the study.

The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.



## 11.6 ENROLLMENT

- 11.6.1 Enrollment activities are performed after patients are screened and may occur prior to or at the same time as the baseline visit.
- 11.6.2 The site should maintain a Patient Screening Log, accounting for the patients who are and are not eligible for the investigation.
- 11.6.3 A patient who meets the inclusion criteria and does not meet the exclusion criteria is eligible to participate in the investigation.
  - 11.6.3.1 If a patient does not meet inclusion or meets exclusion criteria cannot participate in the investigation.
    - 11.6.3.1.1 Record enrollment information (consent and inclusion/exclusion) in the hospital records; complete the Enrollment and Termination Case Report Forms. The CRF must be authorized by the principal investigator or delegate.
    - 11.6.3.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 11.6.4 Inform the eligible patient about the investigation and provide the written consent to the patient.
  - 11.6.4.1 The process of obtaining written consent from an eligible patient needs to comply with the Declaration of Helsinki, International Standards Organization (ISO) 14155-1 and applicable local laws and regulations.
- 11.6.5 Obtain the signature and date from the eligible patient on the ethics committee (EC) approved informed consent.
  - 11.6.5.1 If the eligible patient cannot sign and date the EC approved informed consent him/herself then refer to ISO 14155-1 regarding alternatives for obtaining signature on the informed consent.
  - 11.6.5.2 If an eligible patient does not sign and date the informed consent s/he cannot participate in the investigation. No further protocol activities are performed.
- 11.6.6 Obtain the signature and date from the principal investigator or delegate on the ethics committee (EC) approved informed consent.
- 11.6.7 The patient is enrolled in the investigation when both the patient and investigator signed/dated the informed consent.
  - 11.6.7.1 If there are deviations with regard to obtaining informed consent notify the EC/IRB appropriately.
- 11.6.8 Provide one original signed and dated copy by patient and the principal investigator or delegate to the patient.
- 11.6.9 File the second original appropriately in the Investigator Study Binder (ISB).

11.6.10 Record enrollment information (consent and inclusion/exclusion) in the hospital records, complete the Enrollment Case Report Form. Every effort will be made to notify the sponsor within 5 working days of enrollment. The CRF must be authorized by the principal investigator or delegate.

11.6.10.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

## 11.7 BASELINE VISIT

11.7.1 All Baseline activities are performed after patient is enrolled in the investigation and no more than 60 days prior to undergoing catheter ablation procedure.

11.7.2 The following information will be collected at the baseline visit either from hospital records or through patient interaction:

### 11.7.2.1 Patient Demographics & Physical Examination

- Collect the age;
- Collect the gender;
- Provide the most recent value (within the last month) of the patient height;
- Provide the most recent value (within the last month) of the patient weight; and
- Collect the blood pressure;

### 11.7.2.2 Patient Cardiovascular History

- Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;
- Provide the most recent value (within the last month) of the left ventricular ejection fraction (LVEF) derived from echocardiography or gated nuclear studies; and
- Provide the most recent value of the left atrial size derived from echocardiography.
- Provide the most recent degree of valvular heart disease derived from echocardiography.

### 11.7.2.3 Patient Cardiac Medication

- Identify the drug category of the cardiac medications the patient is taking currently; and
- Document the type of antiarrhythmic the patient was taking in the past to manage AF

NOTE: Patient enrolled should be refractory to at least to one antiarrhythmic medication.

### 11.7.2.4 Patient Medical History

- Indicate the pre-existing cardiac conditions and cardiac procedures; and
- Indicate the non-cardiac medical conditions.

#### 11.7.2.5 Patient Atrial Fibrillation History

- Provide the date (year) the patient first experience AF;
- Provide the average duration of AF episodes;
- Provide the frequency of AF episodes;
- Provide the number of previous Cardioversion for atrial arrhythmias.
- Indicate if the patient experienced any arrhythmias other than AF.

#### 11.7.2.6 Quality of life assessment

- Both the SF-36 and the EQ-5D questionnaire need to be completed, signed and dated by the patient.
- Record the CCS SAF scale.

#### 11.7.2.7 ECG Information

- Provide the information of the most recent ECG performed (heart rate, rhythm on ECG, QT information, general findings).

11.7.2.8 Record baseline visit information in hospital records, complete the Baseline Case Report Forms. Every effort would be made to notify the sponsor within 14 days of the visit. The CRF must be authorized by the principal investigator or delegate.

11.7.2.9 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

#### 11.7.3 Adverse Event (when applicable)

11.7.3.1 Check if any adverse event or adverse device effect occurred.

11.7.3.2 Report the adverse event according to specifications in section “Adverse Event”.

## 11.8 ABLATION PROCEDURE

11.8.1 All patients will undergo catheter ablation using radiofrequency (RF) energy in the cardiac electrophysiology lab as per site practice.

11.8.1.1 Antiarrhythmic medications will be stopped at least 5 half-lives prior to the procedure, except amiodarone, which will be stopped >8 weeks prior to the procedure.

11.8.1.1.1 If antiarrhythmic medications will not be stopped nor amiodarone, this will not be considered as a protocol deviation.

11.8.1.2 Patients may undergo pre ablation CT Scan or MRI imaging of the left atrium as per site practice. If such imaging is performed, presence/absence of pre-existing PV stenosis should be reported in the Ablation Case Report Form.

11.8.1.2.1 If CT Scan or MRI imaging is not performed, this will not be considered a protocol deviation.

11.8.1.3 Patients may undergo pre ablation transesophageal echocardiography as per site practice. If such imaging is performed, and a left atrial thrombus is detected, the ablation procedure should be deferred until thrombus is resolved.

### 11.8.2 Randomization

11.8.2.1 Prior to the ablation procedure, randomize the patient. For the randomization instructions, refer to “Appendix Randomization Instructions”.

11.8.2.1.1 In case the strategy as defined per randomization cannot be performed and a different strategy is used, record the cross over information in the hospital records and complete the Deviation Case Report Forms. The CRF must be authorized by the principal investigator or delegate.

11.8.2.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 11.8.3 Ablation Procedure

11.8.3.1 All procedures will be performed via transseptal access to the Left Atrium (LA).

11.8.3.2 After transseptal access, patients should be anticoagulated with intravenous heparin to maintain an ACT of > 250 sec.

11.8.3.3 A multipolar diagnostic catheter (minimum 4 poles) will be placed in the Coronary Sinus (CS).

- 11.8.3.4 A circular mapping catheter (minimum 10 poles) should be used for both mapping and confirmation of pulmonary vein isolation.
- 11.8.3.5 Ablation will be performed using a market approved open irrigated-tip ablation catheter. In Table 3 the maximum authorized power and irrigation settings are shown. For power and irrigation settings please follow the catheter Instruction for Use (IFU) and the clinical practice.

Table 3 – Irrigated ablation catheter maximum authorized settings.

Irrigated Ablation Catheter Recommended Settings	
Maximum Power	40 W (*)
Maximum Flow Rate	30 mL/min
(*) Lower power settings are recommended on the posterior wall (25-35 W) to avoid the possibility of esophageal injury.	

- 11.8.3.6 Continuous impedance monitoring should be employed and RF should be discontinued if a >10 ohm impedance rise is observed.
- 11.8.3.7 All procedures will be guided using a Cardiac mapping System - Ensite NavX System, St. Jude Medical. The mapping system will be used to construct a three-dimensional reconstruction (shell) of the LA, the PV, the CS, and RA if required. As mapping catheters physicians can use the circular mapping and/or ablation catheters.

**11.8.4 Ablation Strategies**

- 11.8.4.1 A description of each of the three specific catheter ablation strategies is detailed in the following sections:
  - Wide Circumferential Pulmonary Vein Antrum Isolation (PVI) – “Trigger-Based Strategy”, please refer to section 11.8.6.
  - Combined PV Antral Isolation and Ablation of Complex Fractionated Electrograms (PVI+CFE) – “Trigger and Substrate-Based Strategy”, please refer to section 11.8.7.
  - Combined PV Antral Isolation and Empiric Linear Ablation (PVI+Lines) – “Trigger and Substrate-Based Strategy”, please refer to section 11.8.8.

### 11.8.5 Additional Ablation

11.8.5.1 Upon completion of the randomized ablation strategy (whether on the initial or repeat procedure), investigators have the option of either ablating any additional atrial tachycardias or flutters that may arise, or simply cardioverting the patient back to sinus rhythm. Performing a right atrial cavotricuspid isthmus line is allowed in any of the three randomization strategies and will be left to investigator discretion.

11.8.5.2 Any additional ablation lesions performed to treat those tachycardias should be documented in the Ablation Case Report Form.

11.8.5.2.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

11.8.5.3 Performing additional lesions that would involve creating lesions prescribed by one of the other arms of the study is strongly discouraged. For example, if the patient is randomized to PVI+CFE, performing either a roof or mitral line would be strongly discouraged and vice versa.

11.8.5.3.1 If CFE or linear targets (roof or mitral) are performed in an arm which does not include such strategies, complete a Deviation Case Report Form.

11.8.5.3.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 11.8.6 Wide Circumferential Pulmonary Vein Antrum Isolation (PVI) “Trigger-Based Strategy”

11.8.6.1 Through transseptal accesses, the circular mapping and ablation catheters will be advanced into the LA, followed by reconstruction of the LA, PV and CS anatomy using the EnSite NavX.

11.8.6.2 The ostia and the antra of the PV will be defined by:

- Examination of the 3D electroanatomical shell;
- Visualization of the catheter tip entering the cardiac silhouette;
- A decrease in catheter impedance monitored by RF generator;
- Appearance of an atrial potential; and
- Intracardiac echocardiography, when available.

- 11.8.6.3 The circular mapping catheter will then placed sequentially within each of the PV antra to record PV potentials. Circumferential RF lesions will then be placed at least 1-2 cm outside of the PV ostia to encircle and electrically isolate each of the PV antra while avoiding PV stenosis.
  - 11.8.6.3.1 Because of the narrow ridge of tissue between the anterior aspect of the left superior PV and the left atrial appendage, ablation will be allowed within 1 cm of the ostium of the left superior PV to encircle and isolate this vein.
- 11.8.6.4 As each antrum is encircled, the circular mapping catheter should be used to confirm electrical isolation. Isolation of the PV antrum will be considered complete when all PV potentials within each antrum are abolished, as recorded by the circular mapping catheter.
  - 11.8.6.4.1 Ablation tags should only be placed on the LA reconstructed anatomy if RF energy is applied for more than 15 seconds at a given point.
- 11.8.6.5 During PVI ablation, the mean atrial fibrillation cycle length (AFCL) and AF regularity should be measured from a selected CS recording pre-ablation (baseline measurement) and post-ablation.
  - 11.8.6.5.1 The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and dividing 15000 by x.
  - 11.8.6.5.2 The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during ablation should be recorded.
  - 11.8.6.5.3 No intravenous antiarrhythmics should be used during ablation to change AFCL or help regularize/terminate AF.
- 11.8.6.6 If the patient is still in AF at the end of the procedure, electrical cardioversion should be performed to restore sinus rhythm.
  - 11.8.6.6.1 All of the PV antra should be rechecked in sinus rhythm to confirm electrical isolation. If complete isolation has not been achieved, further ablation may be performed to achieve this endpoint.
- 11.8.6.7 Rechecking of each of the PV antra should be performed at the end of the ablation procedure to confirm the presence of block after a minimum 20 minute wait after the last ablation lesion applied to that specific antrum.
  - 11.8.6.7.1 The endpoint is to achieve complete entrance and exit block of all PV antra as recorded by the circular



mapping catheter during sinus rhythm or CS pacing. Exit block should be determined by pacing at high output within the PV and looking for any conduction getting out into the LA. If there is no PV to LA conduction, or capture cannot be obtained anywhere inside the PV, then exit block is fulfilled.

11.8.6.7.2 Termination and/or non-inducibility of AF are not endpoints of this procedure.

11.8.6.8 If the patient is in atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. However, ablation of continuous fractionated electrograms (CFE) and creation of a mitral or roof line are strongly discouraged. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

11.8.6.8.1 If either CFE or mitral/roof lines have been ablated, complete the Deviation Case Report Form.

11.8.6.8.2 Refer to "Appendix Data Collection" for access and information regarding patient data collected for this investigation.

11.8.7 Combined PV Antral Isolation and Ablation of Complex Fractionated Electrograms (PVI+CFE) "Trigger and Substrate-Based Strategy"

11.8.7.1 Patients randomized to this arm will first undergo wide circumferential PVI as described in Section 11.8.6. The endpoint will be complete isolation of all four PV antra as detailed above.

11.8.7.2 Following completion of the PVI procedure, if the patient is in AF, further mapping will be performed to identify regions of CFE with the use of an automated mapping algorithm (EnSite Complex Fractionated Electrograms Algorithm – CFE, St. Jude Medical).

11.8.7.3 Following completion of the PVI procedure, if the patient is not in AF, AF should be induced by rapid atrial pacing from the distal tip of the CS catheter. Pacing should be performed at the shortest 1:1 atrial capture rate for up to 15 seconds at a time, up to 5 times in a row, with 30 seconds between attempts.

11.8.7.3.1 If AF cannot be sustained for longer than 1 min, an infusion of isoproterenol (causing an increase in baseline heart rate > 50%, dose up to 10 mcg/min) can be used to sustain AF. Induced AF must persist for >1 minute prior to mapping for CFE.

11.8.7.4 Once in AF, CFE mapping using the automated algorithm will be performed in the LA, CS, and RA (if needed).

11.8.7.4.1 EGMs should be obtained during AF by mapping with the circular mapping catheter. In areas where the

circular mapping catheter cannot obtain good atrial contact, mapping may be supplemented using the 4 mm tip ablation catheter. Bipolar recordings are to be filtered at 30-300 Hz (default value).

- 11.8.7.5 The detailed technique for mapping/ablating CFE using the automated algorithm has been described and validated previously. In brief, the algorithm measures the time between multiple, discrete deflections (-dV/dT) in a local AF electrogram (EGM) recording over a specified length of time (5 sec) and then averages these inter-deflection time intervals to calculate a mean cycle length (CL) of the local EGM during AF. This mean CL is then projected onto the LA anatomical shell as a color-coded display. The shorter the CL, the more rapid and fractionated the local EGM. Specifically for this study, regions with a mean CL of less than 120 ms will be defined as “CFE” based on previously published data<sup>14</sup>.
- 11.8.7.6 The recommendations and settings for EnSite Complex Fractionated Electrograms Algorithm – CFE is reported in Table 4. If the recommendations and settings are not followed, it is not necessary to complete a Protocol Deviation
- 11.8.7.6.1 At the start of the procedure, the baseline signal noise level should be determined and the P-P Sensitivity limit is to be set just above the noise level (typically 0.03-0.05 mV) to avoid noise detection while allowing detection of low amplitude CFE (often <0.5 mV).
- 11.8.7.6.2 Selectable peak to peak EGM amplitude, EGM width, and post-EGM refractory period are defined to assist in algorithm deflection detection
- 11.8.7.6.3 Width Value and Refractory Value are typically set at 15-20 ms and 35-45 ms respectively to avoid detection of far-field EGMs and to avoid double-counting individual EGM deflections.
- 11.8.7.6.4 To avoid including signals from bipoles that are internal in the LA, the Interpolation Value of the algorithm should be adjusted (no more than 8 mm) to include only those signals obtained from bipoles with good atrial shell contact. CFE sites defined by the algorithm (CL < 120 ms) will be targeted for ablation. Regions with the shortest CL should be targeted first, followed by longer CL regions (up to 120 ms). Ablation at a CFE site shall be continued until the local EGM is eliminated which typically requires 20-60 sec of RF application.
- 11.8.7.7 During ablation of CFE sites, the mean atrial fibrillation cycle length (AFCL) and AF regularity should be measured from a selected CS recording. The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and

dividing 15000 by x. The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during CFE ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during CFE ablation should be recorded. No intravenous antiarrhythmics should be used during CFE ablation to change AFCL or help regularize/terminate AF.

11.8.7.8 The endpoint for CFE ablation is:

- Elimination of all CFE sites in the LA, CS and RA, or
- AF termination.

11.8.7.9 Initially, all CFE sites in the LA and CS should be targeted. If AF does not terminate, CFE in the RA should be mapped and ablated.

11.8.7.10 If AF still does not terminate, sinus rhythm may be restored by electrical cardioversion

11.8.7.11 If AF terminates to sinus rhythm, any remaining unablated CFE sites do not need to be ablated.

11.8.7.12 If AF terminates to an atrial flutter/tachycardia, all remaining CFE sites should be ablated.

11.8.7.13 If AF terminates to an atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

11.8.7.14 However, creation of a roof or mitral line, as outlined in the PVI+Lines strategy, is strongly discouraged.

11.8.7.14.1 If either a mitral or roof line is performed in this randomization arm, complete a Deviation Case Report Form.

11.8.7.14.2 Refer to "Appendix Data Collection" for access and information regarding patient data collected for this investigation.

11.8.7.15 At the very end of the CFE procedure, in sinus rhythm, investigators should place the circular mapping catheter into each of the PV antra to confirm ongoing entrance block and exit block at least 20 min after the last ablation performed in the PVs. If there is PV reconnection, further ablation may be performed to achieve PV antral isolation and to achieve the endpoint of entrance and exit block.

Table 4 - Recommendations and Settings for EnSite CFE Algorithm

<p>As CFE mapping catheter use the circular mapping catheter or ablation catheter in regions where the circular mapping catheter has poor contact.          The circular mapping catheter is preferable. Its electrodes size and electrodes spacing allow increasing the signal quality.</p>		
<p>Assess the baseline noise using the callipers of the DX Landmarking Tools</p>		
Parameter	Value	Parameter definition
P-P Sensitivity	0.03-0.05 mV (Just above the baseline noise)	The P-P Sensitivity control is a minimum peak-to-peak voltage required for the detection algorithm to operate. Incoming signals must be larger than the P-P Sensitivity in order to be considered activation by the system.
Width value	15-20 ms	The Width slider controls the minimum complex width to consider for activation. As CFE maps always use -dV/dt detection type, this parameter indicates the width of the most negative slope. This setting will avoid detection of far-field smooth deflection.
Refractory value	35-45 ms	The Refractory slider controls the minimum amount of time between detections, in order to avoid over counting a single EGM with multiple components.
EGM Segment Length	min 5 s	The Segment Length indicates the total recording duration at each point.
Interpolation value	4-8 mm	The Interpolation slider controls the minimum distance between surface points necessary for the system to interpolate color.
Interior Projection Exterior Projection	4-8 mm	Interior and Exterior Projection are projection sliders that control the Maximum/minimum distance that a 3D Point can project to a location on the interior geometry surface. This setting will avoid collection of EGMs from electrodes that are not in good contact with map shell
Auto-color	ON	The Auto Color toggle controls whether the system automatically controls the pointers on the color bar during DX Landmarking. If Auto Color is enabled, the pointers will adjust to the minimum and maximum data values for all points in the current map.
<p>Set the color-slider so that the orange-red transition occurs around 120 ms.          All regions &lt; 120 msec will be considered "CFE" region. Those region will appear red or white.</p>		
<p>Confirm accuracy of regions labeled as "CFE" by checking EGMs visually</p>		
<p>Target all red-white regions for ablation. This will often require several lesions over "islands" of CFE throughout the atrium. Try to target white spots (the shortest CL) first.</p>		
<p>If CFE ablation in the LA and CS do not terminate AF, map and ablate CFE in the RA.</p>		

### 11.8.8 Combined PV Antral Isolation and Empiric Linear Ablation (PVI+Lines) “Trigger and Substrate-Based Strategy”

11.8.8.1 Patients randomized to this arm will first undergo wide circumferential PVI as described in Section 11.8.6. The endpoint will be complete isolation of all four PV antra as detailed above.

11.8.8.2 Following successful completion of PVI, the patient will undergo empiric linear ablation assisted by the Ensite NavX.

11.8.8.3 All patients randomized to this strategy will undergo ablation of:

- A roof line. Description of the recommended roof line ablation technique is reported in section 11.8.8.7.
- Mitral isthmus line (either posterior or anterior approach). Description of the recommended mitral isthmus line ablation technique is reported in section 11.8.8.8.

11.8.8.4 In general, the use of a stabilizing sheath is suggested to achieve good catheter contact and stability along the path of the linear ablation. Lines can be performed by rotating the sheath (clockwise or counterclockwise) with slight deflection of the catheter. At each point, a minimum of 30 sec of RF should be delivered to achieve local EGM elimination or formation of local double potentials. The catheter can then be moved within 5 mm to the next site on the line.

11.8.8.5 The goal of all linear lesions will be to achieve complete block. Conduction block can only be assessed in sinus rhythm, so cardioversion will be required for testing after the lines are made. If a conduction gap in the line cannot be closed, lesions applied off the line, but adjacent to it, can often close the gap. All lesions do not need to fall exactly on the line. Description of conduction block recommended techniques both for Roof Line and Mitral Isthmus are reported in sections 9.8.8.9. Conduction block should be assessed at least 20 min after the last ablation lesion along the line.

11.8.8.6 During linear ablation, the mean AFCL and AF regularity should be measured from a selected CS recording at baseline and after each line is completed. The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and dividing 15000 by x. The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during ablation should be recorded. No intravenous antiarrhythmics should be used during ablation to change AFCL or help regularize/terminate AF.

#### 11.8.8.7 **Roof Line recommended ablation technique.**

11.8.8.7.1 The goal of the roof line is to connect the superior margins of both superior PVs with a line as cranial as

possible. The line may be performed from left to right or right to left.

11.8.8.7.2 The recommended technique is to have the ablation catheter almost entirely inside the sheath with the distal and proximal poles extending outside of it. The sheath can then be used to position the catheter tip at the margin of the left superior PV lesion set. By dragging the catheter along the roof with gentle clockwise rotation of the sheath, lesions can be delivered, usually with a perpendicular catheter-tissue interface.

11.8.8.7.3 Caution should be exercised to avoid perforation with excessive pressure or power.

#### 11.8.8.8 **Mitral Isthmus Line recommended ablation technique.**

11.8.8.8.1 The mitral isthmus line should be performed using either a posterior or anterior approach.

11.8.8.8.2 **Posterior approach**; the goal is to create a line from the lateral mitral annulus (MA) to the left inferior PV ostium. The catheter is extended through the sheath to the lateral MA (typically close to the distal CS poles) where there is a signal with an A:V ratio of 1:1 or 2:1. The catheter-sheath assembly is then rotated clockwise typically with a perpendicular catheter-tissue interface. The lesions are delivered with clockwise rotation until the left inferior PV ostium is reached. Up to 70% of patients will require ablation within the distal CS to achieve complete block across the MA when using the posterior approach. If block is not achieved, the ablation catheter may be placed in the distal CS. To avoid perforation & circumflex coronary damage, the catheter should be deflected upwards towards the atrial side and power should be limited to 20-25 W. Maximum catheter power settings are reported in Table 4.

11.8.8.8.3 **Anterior approach**; the goal is to create a line from the superior aspect of the MA to the left superior pulmonary vein and/or roof line. Using counter clockwise rotation of the sheath-catheter assembly, the catheter can maintain good anteroseptal wall contact and a line can be created from the MA to the roof line. An anterior approach may also help achieve block when the posterior approach fails.

#### 11.8.8.9 **Pacing Manoeuvres to assess conduction block**

11.8.8.9.1 Once the lines are completed, the patient should be cardioverted and assessment of conduction block should occur at least 20 minutes after the last ablation lesion along the line. In general, pacing from the CS should reveal widely separated double potentials along each of the lines. Single potentials or closely-spaced

potentials with fractionated activity indicate potential gaps and require further ablation.

- 11.8.8.9.2 To assess the **block across the roof line** can be confirmed by demonstrating that the activation sequence of the posterior LA is caudocranial instead of craniocaudal. This can be shown by pacing from the left atrial appendage. If the ablation catheter is placed on the low posterior LA, the pace to local EGM delay will be less than when the ablation catheter is placed in the high posterior LA, closer to the roof line. In the case where the roof line is assessed after creation of a line of block at the mitral annulus, activation of the posterior LA occurs not only low to high, but also right to left (pacing in LAA). Again, you can show this by demonstrating a shorter pace to EGM delay on the right posterior LA compared to the left posterior LA.
- 11.8.8.9.3 To assess the **block across a posterior mitral line**, pacing lateral to the line in the LA appendage from the ablation catheter should result in a proximal-distal activation sequence along the CS. With the ablation catheter still lateral, pacing from the proximal CS should result in a delayed activation in the ablation catheter (usually more than 90-100 msec).
- 11.8.8.9.4 To assess the **block across an anterior mitral line**, place the pacing catheter just lateral to the line and the circular mapping catheter on the high septum, medial to the ablation line. Pacing from the ablation catheter will result in lateral and posterior propagation around the MA with delayed activation in the high septum. As the ablation catheter is moved more laterally, the conduction delay to the septum should shorten. Alternatively, complete linear block can be confirmed if pacing laterally to the line results in a distal to proximal CS activation pattern, while after dragging the catheter to the septal side of the line, the CS is activated from proximal to distal.
- 11.8.8.10 If complete linear block cannot be achieved using a given approach along the mitral annulus, the other approach should be attempted.
- 11.8.8.11 If complete linear block cannot ever be achieved along either line, despite the investigator's best efforts, then this should be documented in the Ablation Case Report Form. This, however, would not be considered a protocol deviation.
- 11.8.8.12 If the patient is in atrial flutter or tachycardia, and the the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and

nature of the additional lesions and/or the cardioversion should be recorded and documented.

11.8.8.13 However, mapping and ablation of CFE in this arm are strongly discouraged. If CFE ablation is performed in this arm, complete a Deviation Case Report Form.

11.8.8.14 Refer to "Appendix Data Collection" for access and information regarding patient data collected for this investigation.

11.8.8.15 At the very end of the PVI+Lines procedure, in sinus rhythm, investigators should place the circular mapping catheter into each of the PV antra to confirm ongoing entrance block and exit block at least 20 min after the last ablation in the PVs. If there is PV reconnection, further ablation may be performed to achieve PV antral isolation to achieve the endpoint of entrance and exit block.

### 11.8.9 Post Ablation Activities

#### 11.8.9.1 Anticoagulation therapy

11.8.9.1.1 All patients will remain anticoagulated with warfarin to maintain an INR of 2-3, or a direct antithrombin inhibitor, for a minimum of 3 months post-ablation.

#### 11.8.9.2 Antiarrhythmic medications

11.8.9.2.1 Antiarrhythmic medications may be continued for the first 3 months following the first ablation to avoid early recurrences. At 3 months, antiarrhythmics must be stopped to assess for clinical recurrence.

11.8.9.2.2 The decision to use antiarrhythmics for the first three months, and the choice of drug, will be left to the discretion of the investigator. However, use of amiodarone for these first three months will not be allowed in the protocol given the long half-life of this medication and the potential for interfering with endpoint assessment at follow-up visits after three months.

#### 11.8.9.3 Post-ablation CT/MRI imaging

11.8.9.3.1 It is recommended, but not mandatory, that patients undergo CT or MRI imaging of the left atrium and of the Pulmonary Veins 3 to 6 months after the last ablation procedure to check for PV stenosis, especially if the patient has symptoms suggestive of PV stenosis.

11.8.9.3.2 If CT Scan or MRI are performed, documentation of the degree of stenosis should be performed. Stenosis less than 50% will be graded as "mild," stenosis 50-69% will be graded as "moderate," and stenosis of 70% or more will be graded as "severe."



- 11.8.10 Record ablation information in hospital records and complete the Ablation Case Report Forms. The CRF must be authorized by the principal investigator or delegate.
  - 11.8.10.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 11.8.11 Collect EnSite NavX study records on a disk, regardless of randomization group. Before copying the disk, make sure that the patient information will not be displayed. To copy the study records to a disk refer to the EnSite System IFU. Patient ID number needs to be reported on the procedure CD/DVD label.
- 11.8.12 Adverse Event (when applicable)
  - 11.8.12.1 Check if any adverse event or adverse device effect occurred.
  - 11.8.12.2 Report the adverse event according to specifications in section “Adverse Event”.

## 11.9 REPEAT ABLATION PROCEDURES

11.9.1 The repeat ablation procedure should employ the identical strategy to the randomized strategy employed during the first ablation procedure.

11.9.1.1 Failure to employ the initial randomized strategy for the repeat procedure will be considered a protocol deviation. In case the strategy as defined per randomization cannot be performed and a different strategy is used, record the cross over information in the hospital records and complete the Deviation Case Report Form. The CRF must be authorized by the principal investigator or delegate.

11.9.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 11.9.2 Blanking Period after the first ablation procedure

11.9.2.1 Based on previously published data<sup>8,11,12</sup>, early recurrence of atrial flutter and/or AF post-ablation may be common in the first 3 months after the procedure and may not predict long-term outcome. Therefore, a 3 month blanking period will be employed after the first procedure as per the HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation<sup>22</sup>. **During this blanking period, recurrences of AF/AT/AFI will not be counted and repeat procedures should not be performed any sooner than 3 months after the first ablation.** Any repeat procedures should be done between 3 and 6 months of the initial procedure.

11.9.2.1.1 If the repeat ablation procedure is not performed between month 3 and month 6, record the information in the hospital records and complete the Deviation Case Report Forms. The CRF must be authorized by the principal investigator or delegate.

11.9.2.1.2 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

11.9.2.2 During the first two months of the blanking period, it is recommended to treat the patient with antiarrhythmic medications.

11.9.2.2.1 If the patient will not be treated with antiarrhythmic medications this will not be considered as a protocol deviation.

11.9.2.3 If a patient has an early recurrence of atrial arrhythmia during the blanking period, it is recommended that the patient be cardioverted and see if arrhythmia consistently recurs before making a decision to perform another ablation.

11.9.2.3.1 If the cardioversion will not be performed this will not be considered as a protocol deviation.

### 11.9.3 Blanking period after the repeat ablation procedure

11.9.3.1 A 3 month blanking period will be employed after the repeat ablation procedure. During this blanking period, recurrences of AF/AT/AFI will not be counted as per the secondary endpoints.

11.9.3.2 During the first two months of the blanking period, it is recommended to treat the patient with antiarrhythmic medications.

11.9.3.2.1 If the patient will not be treated with antiarrhythmic medications this will not be considered as a protocol deviation.

11.9.3.3 If the patient has recurrence of atrial arrhythmia without being treated with antiarrhythmic medications, it is recommended that the investigator may cardiovert and/or start antiarrhythmic drug therapy.

11.9.3.3.1 If the patient will not be treated with antiarrhythmic medications and/or cardioversion will not be performed, this will not be considered as a protocol deviation.

### 11.9.4 Repeat ablation Procedure in the PVI randomization group

11.9.4.1 During the second procedure in the PVI arm, identification of conduction gaps between the PVs and LA should be identified. Gaps should be targeted for ablation to re-isolate the PV antra.

11.9.4.2 The goal should be to re-achieve complete isolation of all PVs from the LA as determined by both entrance and exit block.

11.9.4.3 If the patient is in atrial flutter or tachycardia, and the the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

11.9.4.4 However, performance of either CFE ablation or a mitral or roof line is strongly discouraged. If the patient has a mitral or roof dependent flutter, it is suggested that this may be cardioverted at the end of the procedure. If CFE or a mitral/roof line are performed, complete a Deviation Case Report Form.

11.9.4.4.1 Refer to "Appendix Data Collection" for access and information regarding patient data collected for this investigation.

### 11.9.5 Repeat ablation Procedure in the PVI + CFE randomization group

- 11.9.5.1 During the second procedure in the PVI+CFE arm, identification of conduction gaps between the PV antra and the LA should be identified and targeted for ablation as described above.
- 11.9.5.2 If the patient is not already in AF, AF should be re-induced to identify and ablate any regions of CFE. If CFEs cannot be identified in the LA, CS, or RA, the patient may be cardioverted back to sinus rhythm as during the first procedure.
- 11.9.5.3 If the patient is in atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.
- 11.9.5.4 However, performance of either a mitral or roof line is strongly discouraged. If the patient has mitral or roof dependent flutter, it is suggested that this may be cardioverted at the end of the procedure. If a roof/mitral line are performed, complete a Deviation Case Report Form.
  - 11.9.5.4.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

### 11.9.6 Repeat ablation Procedure in the PVI + Lines randomization group

- 11.9.6.1 During the second procedure in the PVI+Lines arm, identification of conduction gaps between the PV antra and the LA should be identified and targeted for ablation as described above.
- 11.9.6.2 Once PV isolation has been achieved, all of the lines should be checked for conduction gaps. Presence of these gaps may be confirmed by pacing manoeuvres as described in section 11.8.8.9. If conduction gaps are identified, the roof and the MA lines should be reinforced with additional ablation either along the line or immediately adjacent to it until block is achieved.
- 11.9.6.3 If the patient is in atrial flutter or tachycardia, and the the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.
- 11.9.6.4 However, performance of CFE ablation is strongly discouraged. If CFE ablation is performed, complete a Deviation Case Report Form.
  - 11.9.6.4.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

- 11.9.7 Repeat Ablation Procedure for Patients Presenting with Atrial Tachycardia or Flutter Only
- 11.9.7.1 For patients who return for a repeat ablation procedure who have only had recurrence of an atrial tachycardia or flutter, the culprit flutter and/or tachycardia may be targeted. However, the initial randomized strategy should also be repeated as well. Thus, isolation of the PVs should be confirmed and CFE and/or linear ablation should be repeated as applicable..
- 11.9.7.2 If a patient returns in mitral or roof dependent flutter in either the PVI or PVI+CFE arms, performance of a roof or mitral line is strongly discouraged. Every attempt would be made not to perform any mitral or roof line. If a mitral or roof line is performed, complete a Deviation Case Report Form.
- 11.9.7.2.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 11.9.7.3 Right atrial cavotricuspid lines may be performed in any of the three randomized strategies at any time and is left to investigator discretion.
- 11.9.8 Record the repeat ablation information in the hospital records, complete the Repeat Ablation Case Report Form (CRF). Every effort would be made to notify the sponsor within 14 days of the visit. The CRF needs to be authorized by the principal investigator or delegate.
- 11.9.8.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 11.9.9 Collect EnSite NavX study records on a disk, regardless of randomization group. Before copying the disk, make sure that the patient information will not be displayed. To copy the study records to a disk please refer to the EnSite System IFU. Patient ID number needs to be reported on the procedure CD/DVD label.
- 11.9.10 Adverse Event
- 11.9.10.1 As the repeat ablation procedure requires the patient to be hospitalized record the information in the hospital records and complete the Adverse Event Case Report Form. The CRF must be authorized by the principal investigator or delegate.
- 11.9.10.2 Check if any adverse event or adverse device effect occurred.
- 11.9.10.3 Report the adverse event according to specifications in section “Adverse Event”.
- 11.9.10.4 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.

## 11.10 PROTOCOL REQUIRED FOLLOW-UP

11.10.1 Scheduled visits will occur at 3, 6, 9, 12, and 18 months after the first ablation procedure ( $\pm$  14 days for each time point for follow-up). The follow up will occur in the outpatient department of each participating institution.

11.10.2 The Follow Up schedule is summarized in Table 1.

11.10.3 The following information will be collected at the follow up visit either from hospital records or through patient interaction:

11.10.3.1 Physical Examination

- Collect the blood pressure;

11.10.3.2 Recurrence of atrial arrhythmias

- List the atrial arrhythmia episodes the patient experienced since the last visit;
- Classify the episodes; and
- Provide the duration of the episodes;

11.10.3.3 Patient Cardiac Current Medication

- Document a change in cardiac medication therapy since the last visit.

11.10.3.4 ECG Information

- Provide the information from ECG performed during the visit (heart rate, rhythm, QT information and other findings).

11.10.3.5 24 hour Holter

- List the atrial arrhythmia episodes collected by the 24 holter;
- Classify the episodes; and
- Provide the duration of episodes.

11.10.3.6 Quality of Life assessment

- Collect Quality of life measurements using the SF-36 and EQ-5D.
- Record the CCS SAF Scale...
- The quality of life measurement will be assessed at the 6, 12 and 18 months follow up visit.

- 11.10.4 At the time of the last follow-up (18 months), it is recommended that patients have a final standard transthoracic echocardiogram to check left atrial size, valvular heart disease, and ejection fraction.
- 11.10.4.1 If th transthoracic echocardiogram is performed, details of the echocardiographic data should be recorded on the final 18 month Follow Up Case Report Form..
- 11.10.5 Record the follow up information in the hospital records and complete the Follow Up Case Report Form (CRF). The CRF needs to be authorized by the principal investigator or delegate.
- 11.10.5.1 Refer to “Appendix Data Collection” for access and information regarding patient data collected for this investigation.
- 11.10.6 Adverse Event (when applicable)
- 11.10.6.1 Check with the patient if any adverse events or adverse device effect occurred since the last visit.
- 11.10.6.2 Report the adverse event according to specifications in section “Adverse Event”.
- 11.10.7 Patient Death (when applicable)
- 11.10.7.1 If the patient died before the visit took place, report it immediately to the sponsor as indicated in section “Patient Death”.
- 11.10.8 Early Withdrawal (when applicable)
- 11.10.8.1 If the patient decides to withdraw from the investigation for whatever reason, report it immediately to the sponsor as indicated in section "Early conclusion to patient participation".

## **11.11 TRANS TELEPHONIC MONITORING**

- 11.11.1 Patients will be provided with a Trans Telephonic Monitor (TTM) to assess the heart rhythm for the entire duration of the follow-up period.
- 11.11.2 Patients will be asked to send transmissions:
  - 11.11.2.1 Once per week whether or not they are experiencing symptoms to assess for asymptomatic recurrences.
  - 11.11.2.2 Any time they feel any symptom(s) of arrhythmia.
- 11.11.3 If the patient has an implanted device (pacemaker, implantable defibrillator, implantable loop recorder), interrogation of the device will also be used to assess the patient's rhythm where applicable.
- 11.11.4 The TTM will be adjudicated independently by a Core Lab.

## **11.12 QUALITY OF LIFE ASSESSMENT**

- 11.12.1 Quality of life measurements will be performed at baseline, 6, 12, and 18 months after the ablation procedure.
- 11.12.2 The quality of life assessment will be done using the following questionnaires:
  - 11.12.2.1 The 36-item Short-Form Health Survey (SF-36).
  - 11.12.2.2 Euro-QoL 5D (EQ-5D).
- 11.12.3 The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale will be also assessed<sup>26</sup>. For the SAF scale, refer to Appendix L.

## **11.13 COST UTILITY ASSESSMENT**

- 11.13.1 The cost utility of the three ablation strategies will be assessed.
- 11.13.2 A unitary cost per country will be attributed to any hospitalization, repeat ablation procedure, intervention, diagnostic, drug therapy and consultation (GP and/or specialistic visits) that can be referred to the treatment of atrial fibrillation or and that are not required as per protocol.



## **12 RISK DESCRIPTION AND MINIMIZATION**

### **12.1 RISKS**

There is no data suggesting that the risks as reported in section 9.2 Adverse Events is any higher with one technique over the other. In fact, as shown in the STAR AF pilot study<sup>23</sup>, PVI+CFE approach was not associated with any increased risk over PVI alone. Even fluoroscopic exposure times and procedural times were not significantly different between the two arms.

## **13 INVESTIGATION ORGANIZATION**

### **13.1 INVESTIGATION MANAGEMENT**

#### **13.1.1 Sponsor**

The organization, which takes responsibility for the initiation and/or implementation and coordination for the investigation is SJM International, Inc, with offices located at:

St. Jude Medical Coordination Centre BVBA  
Corporate Village, Building Figueras  
Da Vincilaan, 11, Box F1  
B-1935 Brussels  
Belgium  
Tel: +32 2 774 69 37  
Fax: +32 2 774 69 46

The SJM International, Inc., will delegate responsibilities to the local SJM clinical entities in each country.

#### **13.1.2 Sponsor Responsibilities**

Sponsor's responsibilities are in accordance with applicable ISO 14155 guidelines.

It is the responsibility of St. Jude Medical, as the sponsor of the investigation to ensure proper monitoring and compliance with regulatory requirements.

This includes but is not limited to the following activities:

- Select the clinical investigators;
- Activate the study centers after receipt of the required documentation;
- Develop the study database, and perform the analysis;

- Sign off the clinical investigational plan before the start of the investigation or after modifications to the protocol;
- Reviewing collected data and investigation documentation for completeness and accuracy; and
- Ensure that all adverse events and adverse device effect are reported and reviewed with the clinical investigator(s) and where appropriate that all serious adverse events and serious adverse device effects are reported to the relevant authorities and Ethics Committee(s) and or safety monitoring committee(s).

Sponsor personnel or its delegates will not:

- Practice medicine;
- Provide medical diagnosis or treatment to patients;
- Discuss a patients' condition or treatment with a patient without the approval and presence of the health care Practitioner; and
- Independently collect critical study data.

## **13.2 CLINICAL COORDINATING INVESTIGATOR**

The clinical coordinating investigator appointed by St Jude Medical for the STAR AF II investigation is:

Atul Verma, MD FRCPC  
Staff Cardiology, Electrophysiology  
Southlake Regional Health Centre  
712 Davis Drive - Suite 105  
Newmarket, Ontario, Canada, L3Y 8C3  
Phone – 001 905 953 7917  
Fax – 001 905 953 0046  
Email – atul.verma@utoronto.ca

### 13.3 INVESTIGATOR

An investigator is defined as an individual and/or institution responsible for the conduct of a clinical investigation who and/or which takes the clinical responsibility for the well-being of the subjects involved.

#### 13.3.1 Investigator Responsibilities

This investigation will be conducted in accordance with applicable ISO 14155 guidelines, this clinical investigational plan, the signed Agreement, and other agreements applicable laws and regulations and any conditions of approval imposed by the Ethics Committee. To ensure compliance with the guidelines, the sponsor, and independent body, or a regulatory agency may audit the investigation.

By agreeing to this protocol, the investigators and their institutions accept to allow monitoring, audits, Ethics Committee and IRB review, and regulatory inspections that are related to the investigation. They also agree to provide authorized individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate patient consent and patient data confidentiality.

A principal investigator should have experience in and will be responsible for:

- Providing signed Investigator/Co-Investigator (s) Agreement.
- Providing appropriate Ethics Committees Approved Informed Consent.
- Conducting the clinical investigation in accordance with the signed agreement with St Jude Medical, the investigational plan, all applicable laws and regulations (e.g. ISO 14155) and any conditions of approval imposed by the appropriate Ethics Committees or applicable regulatory authorities where the investigation is performed.
- Collection and archiving of data obtained after implant and at follow-up examinations and after the investigation has been completed.
- Strict adherence to the Clinical Investigational Plan testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation.
- Screening and selecting appropriate patients.
- Support the monitor and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. The investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from St Jude Medical.

In addition to the responsibilities of the investigators, the study Coordinating Clinical Investigator will:

- Sign off the final version of the clinical investigational plan and after modifications to the protocol.
- Act as main contact for all study investigators in case of medical questions related to the conduct of the investigation.

### 13.3.2 Investigator Study binder

The investigator will be provided with an Investigator Study Binder (ISB) at the start of the investigation. This file contains all relevant documents necessary for the conduct of the investigation.

All centre data is forwarded to SJM and managed by the clinical project leader (CPL).

Table 5: Centre data collected

Centre Data Collected	Format
EC Approval of Protocol	Paper
EC Approved Patient Informed Consent.	Paper
EC Communication	Paper
Clinical Study Agreement and Exhibits A-E	Paper
Curriculum Vitae site Staff	Paper
Signature and delegation Log	Paper
Initiation Visit Log	Paper

### 13.3.3 Source Data and Patient Files

The investigator has to keep a written or electronic patient file for every patient participating in the clinical investigation. In this patient file, the available demographic and medical information of a patient has to be documented, in particular the following: name, date of birth, sex, height, weight, patient history, concomitant diseases and concomitant medication (including changes during the course of the investigation), statement of entry into the investigation, investigation identification, randomization number, the date of informed consent, all investigational visit dates, predefined performed examinations and clinical findings, observed AEs, and reason for withdrawal from the investigation, if applicable. It should be possible to verify the inclusion and exclusion criteria for the investigation from the available data in this file. It must be possible to identify each patient by using this patient file.

Additionally, any other documents with source data have to bear at least the patient identification and the printing date printed by the recording device to indicate to which patient and to which investigational procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator. All data recorded on the CRF must also be part of the patient's source data.

#### 13.3.4 Record Retention and Archiving

The ISB (Investigator Study Binder) must be safely archived after termination of the investigation.

It is the responsibility of the investigator to ensure that the patient identification logs are stored for at least 15 years beyond the end of the clinical investigation. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the Sponsor.

### **13.4 AMENDMENT PROCEDURE**

Major changes to the protocol will be described in a “CIP Amendment”. The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

The principal investigator will acknowledge the receipt of the amendment and confirm by their signature on the Amendment Signature page that they will adhere to the amendment.

The amendment must be submitted to the relevant EC/IRB and to authorities, where required. Approval from the EC/IRB will be required prior to implementation of the amendment. The approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to St. Jude Medical prior to implementation of the amendment.

Any amendment affecting the patient requires that the patient be informed of the changes and a new consent be signed and dated by the investigator and patient prior to the patient’s next follow-up.

Changes to, or formal clarifications of, the clinical investigational plan will be documented in writing and provided to investigators. This information will be incorporated when an amendment occurs.

### **13.5 BOARDS**

#### 13.5.1 Steering Committee

The STAR AF II Steering Committee is championed by the Coordination Clinical Investigator Dr. Atul Verma, MD FRCPC.

This committee will be actively involved in the investigation, and review its progress at regular intervals. At any time, this committee may request that the investigation be put on hold or even terminated for safety, ethical or other reasons.

#### 13.5.2 Data Safety Monitoring Board

A Data Safety Monitoring Board will be set up specifically to monitor safety data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically.

## 13.6 ETHICAL BASIS

This investigation will be performed in accordance with the World Medical Association Declaration of Helsinki (appendix C), ISO 14155 and all local legal and regulatory requirements.

Prior to start of the investigation, the clinical investigational plan will be submitted together with its associated documents (patient information sheets, patient informed consent forms in the local language) to the relevant Ethics Committee (EC) / Institutional Review Board (IRB) for review.

EC/IRB approval record should clearly identify

- the date of the meeting,
- constitution of the committee and voting members present at the meeting
- the approved version of the clinical investigational plan CIP
- the approved version of the patient information and informed consent.

Approval from the EC/ IRB is necessary prior to the start of the investigation. The original approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to St. Jude Medical prior to the first investigational assessment.

Any amendments to the protocol should be submitted to the relevant EC/IRB.

EC/IRB will be informed about SAEs and UADEs in accordance with local and national requirements.

## 13.7 INSURANCE

St. Jude Medical as Sponsor of this investigation has a general liability insurance for this investigation in accordance with the requirements of applicable local laws.

## 13.8 MONITORING

It is the responsibility of St Jude Medical as the sponsor of the investigation to ensure proper monitoring of the investigation and to ensure that the investigation is conducted, recorded and reported in accordance with the Clinical Investigational Plan, the signed Clinical Study Agreement, and the applicable laws and regulations.

Monitoring will be conducted at the centers participating in the investigation according to the standard operating procedures and work instructions.

### 13.8.1 Center Data

Center data will be reviewed for completion and regulatory compliance.

### 13.8.2 Patient Data

In line with ISO 14155 guidelines, monitoring will include verification of data entered in the CRF against original patient records. This verification will be performed with direct access to the original patient records. The Sponsor guarantees that patient confidentiality will be respected at all times. Participation in this investigation will be taken as agreement to permit direct source data verification.

Patient data will be reviewed for accuracy, quality and protocol adherence. Additionally patient safety will be evaluated.

### 13.8.3 Monitoring Activities

An overview of the monitoring activities is shown in Table 6.

Table 6 : Monitoring Activities

Visit Type	Prompted By	Scope of Visit	
Initiation	<ul style="list-style-type: none"> <li>○ Receipt of essential documents for centre by SJM</li> <li>○ Ethics Committee (EC) approval of Protocol</li> <li>○ EC approved Patient Informed Consent (PIC)</li> <li>○ Agreement plus exhibits completed, signed and dated by the centre</li> </ul>	No patient data	<ul style="list-style-type: none"> <li>○ Train staff participating in the investigation</li> <li>○ Collect outstanding center and staff documents</li> </ul>

Visit Type	Prompted By	Scope of Visit	
Periodic	<ul style="list-style-type: none"> <li>○ Enrollment of minimum, 3 patients at the centre</li> <li>○ Enrollment of greater than 10 patients at the centre</li> <li>○ Verification of critical data before database freeze and analysis</li> <li>○ Patient data quality issues identified at the centre</li> <li>○ Regulatory issues identified</li> <li>○ Safety Issues identified</li> </ul>	<ul style="list-style-type: none"> <li>○ Review patient's consent</li> <li>○ Review patient data as compared to source document</li> <li>○ Generate DCFs for missing and/or inaccurate patient data recorded on the CRFs</li> <li>○ Review adherence with the protocol</li> </ul>	<ul style="list-style-type: none"> <li>○ Resolve outstanding issues from previous monitoring visits</li> <li>○ Review ISB for completeness</li> <li>○ Identify issues</li> <li>○ Meet with delegated centre staff to review and resolve issues and DCFs in a report</li> <li>○ Record visit, outstanding issues and DCFs</li> <li>○ Retrain staff (centre &amp; SJM) conducting the investigation when necessary</li> </ul>
Close Out	<ul style="list-style-type: none"> <li>○ All patients enrolled at centre completed participation in the protocol</li> </ul>	<ul style="list-style-type: none"> <li>○ Review patient's consent</li> <li>○ Review patient data as compared to source document if necessary</li> <li>○ Generate DCFs for missing and/or inaccurate patient data recorded on the CRFs</li> <li>○ Review adherence with the protocol</li> </ul>	<ul style="list-style-type: none"> <li>○ Resolve outstanding issues from previous monitoring visits</li> <li>○ Review investigation site binder</li> <li>○ Identify issues</li> <li>○ Meet with delegated centre staff to review issues and DCFs</li> <li>○ Resolve all issues and DCFs</li> <li>○ Meet with investigator to discuss record retention and archiving; and final communication to the EC regarding the close of the investigation</li> <li>○ Record visit in a report</li> </ul>



#### 13.8.4 Designated monitors

Monitors are individuals, trained and qualified to ensure quality of the data and confirm adherence to the clinical investigational plan and clinical research agreement.

#### 13.8.5 Internal Quality Assessment

An investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized SJM employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

The purpose of the internal quality assessment is to determine whether the evaluated activities were appropriately conducted and the data were generated, recorded, analyzed and accurately reported according to the Clinical Investigational Plan, the signed Clinical Study Agreement, the Standard Operating Procedures (SOPs) and the applicable laws and regulations.

#### 13.8.6 Competent Authority (CA) Inspections

The investigator and/or designate should contact St. Jude Medical immediately upon notification of impending CA inspection. A clinical monitor will assist and immediately review investigational documentation with the investigator and/or designate to prepare for the audit.

An investigator who has authority to grant access shall permit authorized CA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where procedures are held (including any establishment where procedures are used or where records or results are kept).

An investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized CA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

An investigator shall permit authorized CA employees to inspect and copy records that identify patients, upon notice that CA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the sponsor or EC/IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

### **13.9 STUDY REPORT AND PUBLICATION POLICY**

After conclusion of the investigation, an integrated clinical and statistical report shall be written by the Sponsor in consultation with the clinical coordinating investigator.

The first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by the Sponsor. The Sponsor is entitled to delay publication in order to obtain patent protection. For more details regarding publications, refer to the publication Agreement.

### 13.10 SPONSOR CONTACTS

Contact	Telephone
<b>Christophe Bailleul</b> VP of Clinical Operations International Division	<a href="mailto:cbailleul@sjm.com">cbailleul@sjm.com</a> phone: +32 2 774 6958
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## **APPENDIX A: ABBREVIATIONS**

<b>Abbreviation</b>	<b>Description</b>
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFCL	Atrial Fibrillation Cycle Length
AHA	American Heart Association
AT	Atrial Tachycardia
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CCS SAF	Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale
CFE	Complex Fractionated Electrograms
CIP	Clinical Investigation Plan
CL	Cycle Length
CPL	Clinical Projects Leader
CRA	Clinical Research Associate
CS	Coronary Sinus
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form

Abbreviation	Description
ESC	European Society of Cardiology
ECG	Electrocardiogram
EGM	Intracardiac Electrograms
EQ-5D	EuroQol Group 5-Dimension
FU	Follow Up
GP	General Practitioner
HV	High Voltage
ICD	Implantable Cardioverter Defibrillator
INR	International Normalized Ratio
IFU	Instruction for Use
IRB	Institutional Review Board
ISB	Investigator Study Binder
LA	Left Atrium
MA	Mitral Anulus
MRI	Magnetic Resonance Imaging
PIC	Patient Informed Consent
PVA	Pulmonary Vein Antrum
PVI	Pulmonary Vein Isolation
PTCA	Percutaneous Coronary Angioplasty
RA	Right Atrium
SAE	Serious Adverse Event

Abbreviation	Description
SF 36	Short Form 36
SMF	Site Master File
SOP	Standard Operating Procedures
SJM	St. Jude Medical
TEE	Transesophageal echocardiogram
TTM	Trans Telephonic Monitor

## **APPENDIX B: REFERENCES**

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## **APPENDIX C: DECLARATION OF HELSINKI**

### **WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

#### **A. INTRODUCTION**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve

preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

## **B. PRINCIPLES FOR ALL MEDICAL RESEARCH**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information

about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified

individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
  - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
  - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

## **APPENDIX D: LABELLING/ MANUALS**

The manuals for the EnSite NavX may be found on-line at [www.simplprofessional.com](http://www.simplprofessional.com) and should be consulted.

## **APPENDIX E: SYNOPSIS**

### **Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial – Part II. STAR AF II**

#### **Background**

To date, there is no randomized, multicenter trial addressing the best approach to AF ablation in persistent AF. It is unclear if PV antral isolation (PVI) is sufficient as alone strategy for persistent AF.

Furthermore, if additional substrate ablation is to be added, it is unclear if linear (PVI+Lines) or CFE ablation (PVI+CFE) should be the first choice approach. Thus, there is a good rationale for determining the best approach to AF ablation in patients with persistent AF.

#### **Hypothesis**

This investigation is designed with the hypothesis that combined PV Antral Isolation and Ablation of Complex Fractionated Electrograms (PVI+CFE) approach will offer a higher success rate compared to the Wide Circumferential Pulmonary Vein Antrum Isolation (PVI) approach and to the Combined PV Antral Isolation and Empiric Linear Ablation (PVI+Lines) approach.

#### **Inclusion / Exclusion Criteria**

##### **Inclusion Criteria**

- Patients age is 18 years or greater;
- Patients undergoing a first-time ablation procedure for AF;
- Patients with persistent AF - Persistent AF will be defined as a sustained episode lasting > 7 days and less than 3 years.
- Patients with symptomatic AF that is refractory to at least one antiarrhythmic medication - Symptomatic patients are those who have been aware of their AF at anytime within the last 5 years prior to enrollment. Symptoms may include, but are not restricted to, palpitations, shortness of breath, chest pain, fatigue, left ventricular dysfunction, or other symptoms, or any combination of the above.
- At least one episode of AF must have been documented by ECG, holter, loop recorder, telemetry, trans telephonic monitoring (TTM), or implantable device within last 2 years of randomization in this investigation;
- Patients must be able and willing to provide written informed consent to participate in this investigation; and
- Patients must be willing and able to comply with all peri-ablation and follow-up requirements.

Exclusion criteria:

- Patients with paroxysmal AF - Paroxysmal AF will be defined as a sustained episode lasting < 7 days.
- Patients with long-standing persistent AF - Long-standing persistent AF will be defined as a sustained episode lasting more than 3 years.
- Patients for whom cardioversion or sinus rhythm will never be attempted/pursued;
- Patients with AF felt to be secondary to an obvious reversible cause;
- Patients with contraindications to systemic anticoagulation with heparin or coumadin or a direct thrombin inhibitor;
- Patients with left atrial size  $\geq 60$  mm (2D echocardiography, parasternal long axis view); and
- Patients who are or may potentially be pregnant.

**Investigation Design**Type

This investigation is a prospective, randomized, parallel, single-blind and multicenter design.

Randomization

- Randomization is stratified by center.
- Patients will be randomized 1:4:4 into one of three arms:
  - Pulmonary vein antrum isolation (PVI) alone;
  - PVI plus ablation of complex fractionated electrograms (PVI+CFE); and
  - PVI plus empiric linear ablation (PVI+Lines).

**Endpoints**Primary Endpoint

- Freedom from documented AF episodes > 30 seconds at 18 months after one or two ablation procedure with/without antiarrhythmic medications.

Secondary Endpoints

- Freedom from documented atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Freedom from documented atrial flutter and atrial tachycardia episodes > 30 seconds at 18 months after one and two procedures with/without antiarrhythmic medications;
- Freedom from any atrial arrhythmia (documented or not) episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Freedom from symptomatic AF episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Freedom from symptomatic atrial arrhythmia episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications;
- Incidence of peri-procedural complications, including stroke, PV stenosis, cardiac perforation, esophageal injury and death.
- Procedure duration;



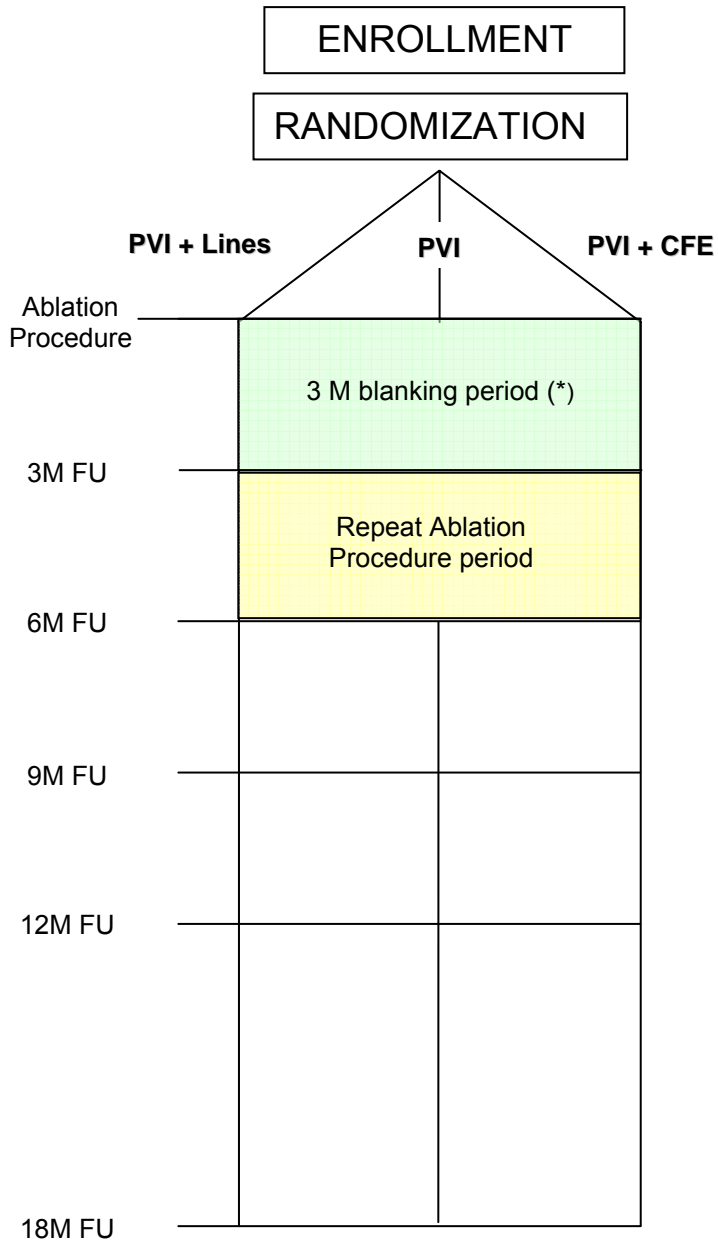
- Fluoroscopy time;
- Number of repeat procedures;
- Effect of each strategy on AF cycle length/regularity/termination;
- Relationship of acute termination of AF to long-term procedural outcome;
- Percentage achievement of complete linear block in linear ablation arm;
- Effect of complete linear block on procedural outcome in linear ablation arm;
- Quality of life measurements (SF-36, EQ-5D and CCS SAF) at baseline, 6, 12 and 18 months after one and/or two ablation procedures;
- Correlation of AF burden to symptoms and quality of life changes;
- Improvement in AF burden by > 90% post ablation procedure;
- Relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome;
- Cut off of AF burden that affects the Quality of Life measurement.
- Evaluation of cost effectiveness; and
- Mortality

### **Enrollment Target**

The enrollment target for this investigation is 549 patients.

The patient will participate in this investigation for 18 months from enrollment to the last follow-up.

**Project Flow**



(\*) During the 3 months blanking period the AF/AT/AFL recurrence will not be taken into account.

### **Follow-Up Procedures**

Follow Up visits will be performed according to Table 1 regardless of randomization group:

(\*) This is **only to be performed when applicable**.

	<b>When</b>	<b>Window</b>	<b>Activities</b>
Enrollment	Within 30 days before or during Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Eligibility</li> <li>• Patient Informed Consent</li> </ul>
Baseline Visit	Within 60 days before Ablation Procedure	Not Applicable	<ul style="list-style-type: none"> <li>• Patient Demographics &amp; Physical Examination</li> <li>• Patient Cardiovascular History</li> <li>• Patient Current Cardiac Medications</li> <li>• Patient Medical History</li> <li>• Patient AF History</li> <li>• 12 Lead ECG Information</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
Ablation Procedure	Within 60 days after Baseline Visit	Not Applicable	<ul style="list-style-type: none"> <li>• Randomization</li> <li>• Ablation Procedure Data Collection</li> <li>• Adverse Events(*)</li> </ul>
1st protocol follow-up	91 days after first Ablation Procedure (3 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events (*)</li> </ul>
Repeat Ablation Procedure	between day 91 – 183 (after first Ablation Procedure)	Not Applicable	<ul style="list-style-type: none"> <li>• Ablation Procedure Data collection</li> <li>• Adverse Events(*)</li> </ul>
2nd protocol follow-up	183 days after first Ablation Procedure (6 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
3rd protocol follow-up	274 days after first Ablation Procedure (9 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Adverse Events(*)</li> </ul>

	When	Window	Activities
4th protocol follow-up	364 days after first Ablation Procedure (12 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>
5th protocol follow-up	547 days post first Ablation Procedure (18 Months)	± 14 days	<ul style="list-style-type: none"> <li>• AF/AT Recurrence Assessment</li> <li>• Patient Current Cardiac Medications</li> <li>• 12 Lead ECG</li> <li>• 24 Hour Holter</li> <li>• Quality of Life Assessment (SF-36, EQ5D and CCS SAF)</li> <li>• Adverse Events(*)</li> </ul>

## APPENDIX F: DATA COLLECTION

### CRF completion per visit

**X** It is **mandatory** to complete this CRF for this activity

**(X)** This is **only to be completed when applicable**.

	ENR	BASE	ABL	RE-ABL	FU	QoL	AE	DEV	DEATH	TERM
Enrollment	X						(X)	(X)	(X)	(X)
Baseline Visit		X				X	(X)	(X)	(X)	(X)
Ablation			X				(X)	(X)	(X)	(X)
Redo Ablation (within Blanking period)				X			X	X	(X)	(X)
3 M FU					X		(X)	(X)	(X)	(X)
Redo Ablation (between 3 – 6 Months)				X			X	(X)	(X)	(X)
6 M FU					X	X	(X)	(X)	(X)	(X)
Redo Ablation (after 6 Months)				X			X	X	(X)	(X)
9 M FU					X		(X)	(X)	(X)	(X)
12 M FU					X	X	(X)	(X)	(X)	(X)
18 M FU					X	X	(X)	(X)	(X)	(X)
Death							X		X	X

## **APPENDIX G: DATA COLLECTION METHOD**

Electronic data capture (EDC) will be used for this investigation, therefore please find below instructions on how to access and use the Electronic Case Report Form (eCRF) application.

Worksheets will be provided to assist in the collection of the data. The use of the worksheet is required.

### **Access to eCRF application**

The eCRF application is accessed through the internet and requires the use of a personal user name and password.

The following are required prior to receipt of Personal user name and password

- CV;
- Completed signature and delegation form;
- Documented Training; and
- Email address and telephone

Personal user name and password are provided by email. The first time the eCRF is accessed, the password will need to be changed.

If password is forgotten or lost, a new password will be provided by email by following the instructions on the webpage.

Each centre must be authorized to start enrolling patients in the investigation before access privileges to the eCRF application are made available.

Access privileges are based on the tasks assigned on the signature and delegation form and will be either:

- reviewing and data entry; or
- reviewing, data entry and signature

### **Worksheets**

Worksheets are provided to assist in collection of the data. When the worksheets are used, they need to be signed and dated and reside with the hospital records. If the worksheets are not used, hospital records must reflect and support all the information entered onto the eCRF.



# ST. JUDE MEDICAL™

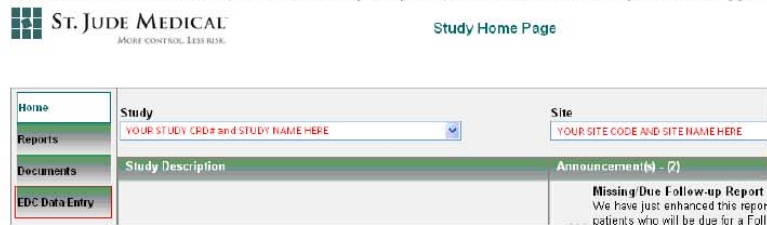
## RDC OnSite Tip Card

- For protocol related questions please contact your FCE or project team.
- For any technical issues with RDC OnSite please call our toll free help line at 866-593-2910 or send an e-mail to [EDC@sim.com](mailto:EDC@sim.com).

### Logging Into RDC OnSite:

1. Click on the SJM Portal link provided to you by email. Enter your username and password. Pressing "Enter" will take you to the Study Site Portal. Click on the link to access the SJM Study Site Portal, where you can access information regarding your Study/Site.
2. Select the appropriate Study and Site Name from the dropdown menus. Pressing "Go" takes you to the Portal Study Home Page. **NOTE:** Applies to users with multiple SJM EDC studies. Users with access to a single EDC study are taken directly to the Portal Study Home Page upon entry.
3. Locate the "EDC Data Entry" hyperlink on the left side. Clicking this hyperlink launches a new web browser opened to the RDC OnSite login screen.
4. Enter your Username and password again. You will be taken to the RDC OnSite Home Page where you can begin working with your study.

**NOTE:** Only one RDC OnSite session window can be open at a time. If you try to open additional sessions you will be logged out of any open sessions.



### Opening a Subject Casebook / Case Report Form (CRF):

1. From the RDC OnSite Home Page mark the checkbox under the "Select" column for each subject casebook to be viewed.
2. Select from the "Select Patients and..." dropdown menu field the "Open Patient Casebook" option and press "Go". You will be taken to the Casebook Page, where each selected subject casebook will be listed in table format.
3. From the Casebook Page click a CRF icon to open the CRF. A new web browser window will open known as the Data Entry Window (DEW).
4. If required, change the Study Visit by selecting it through the "Visit" dropdown menu.

### Routing Discrepancies to your FCRA / CRA – DEW Navigator Pane:



Route Discrepancies to your FCRA / CRA for resolution when:

- Data changes for Automated Edit Checks still violate Edit Check Rules; and
- Addressing manually entered Discrepancies.

1. Expand the Navigator Pane by clicking on the arrow on the right-edge of the DEW.
2. Click on an Active Discrepancy within the List sub-pane.
3. Review the Discrepancy Description within the Details sub-pane to assess the appropriate action. Change data on the CRF if required.
4. At the bottom of the Navigator Pane locate the "Action" dropdown menu field and select the "Send to CRA" option. Press "Go".
5. In the Discrepancy Action – Send to CRA dialogue window enter a Comment and press "OK" to route the Discrepancy to the FCRA / CRA.
6. After all CRF activities are completed save your changes by pressing the "Save" icon. Click the DEW Close icon "X" to return to the Casebook Page.

### Adding Scheduled and Unscheduled CRFs to a Study Visit – Casebook Page:



- **Add Visit Page** – Adds CRFs scheduled for the Study Visit (eg, another Implant form).
- **Add Other Page** – Adds CRFs not scheduled for the Study Visit (eg, an AE form to a 6-Month visit).

1. Mark the checkbox for the Subject casebook you want to add the CRF to and press either the "Add Visit Page" or "Add Other Page" button to open the appropriate dialogue window.
2. In the dialogue window select the radio button for the CRF to be added. Press the "Continue" button.
3. In the dialogue window the CRF sub-visit field will automatically be set to the next available number, therefore, you won't need to change it (for Add Visit Page only). Press the "Apply" button to continue. The CRF icon will appear in the Study Visit.
4. **If the CRF was added in error** and no data was saved onto the form, press the "Refresh" button and the CRF will be removed from the Study Visit.

**NOTE:** Add Visit Page can be used only after data entry is started on at least one scheduled CRF in that Study Visit.



Version 1.1, September 25, 2009



**Summary of Casebook Status Icons – Home Page**

	No Data Entry is started.
	At least some Data Entry is saved. No Open Discrepancies.
	At least some Data Entry is saved. Active Discrepancy present on at least one CRF requiring current user's attention. May also include Other Discrepancies.
	At least some Data Entry is saved. Other Discrepancy present on at least one CRF requiring current user's attention. No Active Discrepancies present.

**Summary of CRF Status Icons – Casebook Page**

	CRF not started. Data entry is expected.
	Save Incomplete CRF – The CRF was started and only the Visit Header Date was completed.
	Save Incomplete CRF – Data Entry is incomplete. User is not done inputting all the data, and will finish at a later time.
	Save Complete CRF – Data Entry is complete. User has met all the requirements for the form, and the responses are considered complete. Automated Discrepancy Edit Checks are activated. CRF has no open issues.
	Save Complete CRF – Data Entry is complete. CRF contains Other Discrepancies that another user group must address.
	Save Complete CRF – Data Entry is complete. CRF contains Active Discrepancies that the current user group must address.
	*Approved CRF – CRF Data responses have been approved by an investigator. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	*CRF requires Re-Approval – Looped arrow next to signature indicates Data, an Investigator Comment, and/or Discrepancy was updated since the CRF was Approved. (If Open Discrepancies are present, the icon would also be red or yellow.)
	Verified CRF – CRF Data responses are verified against source documents. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Active Discrepancies present.
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Other Discrepancies present.
	*CRF is Verified and Approved – CRF Data responses are verified against source documents by the FCRA / CRA, and the Data responses approved by the Principal Investigator.
	CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Active Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Other Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF at Pass 2 Complete. This icon indicates Data Entry was completed by the sponsor in-house using data submitted on paper CRFs.

\*APPROVAL FEATURE CURRENTLY AVAILABLE TO INVESTIGATORS FOR THE DEATH CRF ONLY.

**Summary of Discrepancy Status Icons – Data Entry Window (DEW) Navigator Pane**

	Active Discrepancy that the current user group must address.
	Other Discrepancy that another user group must address.
	Resolved Discrepancy requiring no further action by any user group.

**NOTE:** Obsolete Discrepancies due to Data updates or Validation Procedure / Automated Edit Check updates will be removed from the List sub-pane.

**Summary of Data Entry Window (DEW) Toolbar Icons**

	Add Discrepancy		Delete Row		Approval History		*Print		First/Previous Page		Close
	Investigator Comment		Verification History		Approval		Save		Next/Last Page		

**DO NOT USE THESE TOOLBAR FUNCTIONS**

**Helpful Hints:**

- CRF Deletions** – If a CRF with saved data requires deletion notify your SJM contact, providing information about the form.
- Refresh** – Press the "Refresh" button to refresh RDC OnSite with current information (statuses, etc.)
- Printing a Subject Casebook / CRF** – Go to the RDC OnSite Report Page to print a Patient Data Report. Report types include casebooks with saved Subject data and blank Subject casebooks.
- Logout** – Use the web browser close icon "X" to exit. To re-enter, navigate through the SJM Portal.



## **APPENDIX H: RANDOMIZATION INSTRUCTIONS**

Before calling St. Jude Medical's (SJM) Automated Randomization System, you must have the following available:

1. Your 4-digit Authorization Code that will be provided by SJM
2. SJM Patient ID number.

You must call the SJM Automated Randomization System via a touch-tone telephone set, by calling the toll free number reported in the table below:

<b>Toll Free Numbers</b>	
<b>US and Canada</b>	<b>(800) 219-7285</b>
<b>Outside US or Canada</b>	<b>+1 (818) 493-2265</b>

To complete the randomization process, follow the instructions as you will hear by phone.

## **APPENDIX I: PATIENT INFORMATION SHEET AND PATIENT INFORMED CONSENT**

### **Patient Information Sheet Template**

#### **PATIENT INFORMATION SHEET**

### **Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial – Part II STAR AF II**

**<Name of the Investigator>**

**<Centre Address>**

**<Telephone Number>**

Dear Patient,

You are invited to take part in a research investigation. Before you decide on participating in this clinical trial, we would like to explain to you why we consider this research project is important and what it involves. Please take time to read the following information carefully and discuss it with your doctor. Ask your doctor if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The research is organized and funded by a medical company. This medical company is SJM international, Inc. The research is coordinated by:

St Jude Medical Coordination Centre  
The Corporate Village  
Building Figueras  
Da Vincilaan 11, Box F1  
1935 Zaventem  
Belgium

#### **What is the purpose of this investigation?**

The purpose of this research study is to collect information regarding the safety and efficacy of three different techniques used to treat atrial fibrillation. Atrial fibrillation is an abnormal heart rhythm in which the top chamber of your heart (the atrial chamber) beats very fast. The procedure performed to treat atrial fibrillation involves placing several catheters (long thin round solid tubes capable of conducting electricity to and from your heart) in your heart and heating the tip of one of these catheters to damage the tissues in particular regions of the atrium. These tissues are known to be responsible for your atrial fibrillation. This procedure is now being practiced at many hospitals and is not in itself experimental. Different techniques have been developed to eliminate atrial fibrillation by ablation. One technique targets tissues around the pulmonary veins (blood vessels that bring blood from the lung to the heart) where “triggers” for atrial fibrillation may be located. Another technique targets not only

targets the “triggers” described above, but also special areas around the atrium which are critical to causing atrial fibrillation to continue, characterized by certain signals (known as “complex fractionated electrograms” or “CFE”). A third technique targets the “triggers” as described above, but also modifies the atrium so that it cannot go into atrial fibrillation by creating lines of ablation in specific areas.

In all three techniques, a virtual positioning system similar to GPS (Global Positioning System) allows your doctor to track the position of the catheter(s) in your heart. All of the techniques have now been extensively studied individually, but they have never been compared against one another. The study will compare the occurrence of atrial fibrillation following ablation performed using either a trigger-based technique, a trigger-based technique plus CFE ablation, or a trigger-based technique plus ablation lines.

### **Conduct of the investigation**

A total of 549 patients will take part in this investigation which is expected to last approximately 3 years and is being conducted in up to 30 centers in Europe, Canada, Asia and Australia. Each patient will participate in the study for a period of 18 months.

If you decide to participate in this investigation, you will need to sign this document and you will be enrolled in the investigation.

Your physician has already determined that you need atrial fibrillation ablation. If you agree to participate in this study, you will be randomly (the same as flipping a coin) assigned to one of the three techniques used to achieve ablation of atrial fibrillation. You have a 1 out of 9 chance of having the trigger-based ablation procedure, a 4 out of 9 chance of having a trigger-based procedure plus CFE, and a 4 out of 9 chance of having a trigger-based procedure plus lines. You will then be followed by your physician/registered nurse at 3 months, 6 months, 9 months, 12 months, and 18 months.

Before the procedure, you will be asked to complete a Quality of Life questionnaire as well as have an echo test completed to measure heart function parameters.

The first follow up visit will be scheduled 3 months after the procedure. During this visit you will complete another questionnaire and be asked to wear a 24 hour heart monitor called a Holter monitor. The subsequent study visits will be the same, occurring at 6, 9, 12, and 18 months after the procedure.

You will also be asked to wear a special monitor that can transmit your heart rhythm over the telephone every time you press a button called a transtelephonic monitor (TTM). You will be asked to wear the TTM for the whole duration of the investigation. You will be asked to press the button on your TTM any time you feel any symptoms that you think may be atrial fibrillation. You will also be asked to press the button at least once a week when you are feeling well. This monitor is designed to be worn for long periods of time and you will be given information on how to put it on and take it off and how to operate it.

At the end of the study, you will continue to be followed in accordance with local practice.

### **Do I have to take part?**

Your participation in the investigation is completely voluntary, will not cost you anything and you will not be paid. If you decide to take part, you will be given this information sheet to keep and be asked to sign this form on the last page. If you

decide to take part, you are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

**What are the possible disadvantages and risks of taking part?**

The risks of atrial fibrillation ablation include: a small risk of bleeding or infection where the catheter enters the skin (less than 2%); a risk of perforating a hole in your heart which could require urgent drainage or urgent surgery (less than 2%); a risk of stroke (less than 1%); a risk of pulmonary vein stenosis, or narrowing of any one of the blood vessels that brings blood back to your heart causing permanent shortness of breath (less than 2%); and a risk of damaging the esophagus, or foodpipe, which lies right behind the heart (less than 0.1%). If the esophagus is damaged, a small connection can form between the heart and the esophagus, called a fistula, and this complication is almost always fatal (less than 0.1%).

There is no data suggesting that the risk of any of the above complications is any higher with one technique over the other.

There are no additional risks above and beyond undergoing atrial fibrillation ablation outside of the study if you choose to participate.

**What are the possible benefits of taking part?**

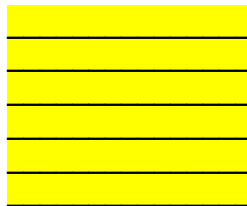
There may be no benefits to you for participating in this study. Medical science may benefit from your participation which may lead to benefits for future patients with this condition. Your participation may also contribute to the creation of new diagnostic tests, new medicines or other procedures that may have commercial value. However, your participation in this study will not entitle you to a share in any future economic benefits.

**What if new information becomes available?**

If significant new information is found during the study, you and your doctor will be given the information as soon as possible for review and discussion. The information could affect whether you continue to participate. If changes are made to the study or new findings develop during the course of the research, which may impact on your willingness to continue, you will be given relevant details and, if necessary, your consent will be requested again

**Will you be insured?**

The sponsor of this investigation concluded a special insurance for your participation: The insurance details are:



**Will my taking part in this investigation be kept confidential?**

If you consent to take part in the investigation, the information collected from your participation is considered as personal data. In order to check the data, it will be necessary to compare the data with your medical records. The sponsor, its representatives and sub-contractors, research team members and study monitors and regulatory agency staff may look at your study related medical records. All these people are obliged to observe strict confidentiality when handling the data or are bound by professional secrecy codes. Your name will **NOT** be disclosed outside the hospital.

Your personal data will be processed electronically to determine the outcome of the investigation. Your identity will be coded to preserve your anonymity. The data collected will be sent to the sponsoring company (in Belgium) for analysis.

Your data may be transferred to other countries where data privacy laws are less strict than those of European Union.

In accordance with the laws relating to data protection, you will be able to exercise your rights to access your personal data and to have any justifiable corrections made. If you wish to do so, you should request this from the doctor conducting the investigation.”

In participating in the investigation, you authorize the sponsoring company to use the information obtained during the investigation for scientific communications and publications.

If you agree, your General Practitioner will be informed of your participation in this investigation.

**What will happen to the results of the research investigation?**

The results will be analyzed for the purpose of publication in scientific journals without disclosing your identity.

**Contact for further information**

If you have any problems, concerns, questions or complaints about this investigation, you should preferably contact

Dr. \_\_\_\_\_ on \_\_\_\_\_.

Thank you for taking the time to think about taking part in this investigation.

If you agree to take part in this investigation, please complete and sign two of these documents on the last page together with your doctor. One signed document is for you, the other one will remain at this hospital.

This patient information consent form has been approved by

(enter EC name/details)

on

(enter date approved).

**Patient Information Consent Template**

**PATIENT INFORMED CONSENT (PIC)**

**Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial – Part II**  
**STAR AF II**

1. I understand that my participation is voluntary.
2. I understand that I am free to refuse to participate in the proposed investigation, without giving any reason and without my medical care or legal rights being affected.
3. I understand that I am free to withdraw from the proposed investigation at any time, without giving any reason, without my medical care or legal rights being affected.
4. I understand that anonymized data collected during the investigation prior to the withdrawal will be used in the analysis and communicated in publications.
5. I confirm that I have read and understand the information presented for the investigation and have had the opportunity to ask questions.
6. I agree to participate to the proposed investigation and to comply with the procedures related to it.
7. I give my permission to have my general doctor informed of my taking part in the investigation.
8. I give my permission that sections of any of my medical notes may be inspected by people from the company, company’s representatives, the ethics committee and regulatory authorities.

**2 copies of this consent form must be signed and dated by you and the investigator:**

**You will receive one copy of the Patient information sheet and the patient informed consent form and 1 copy is for the investigator to be filed in the investigator study binder.**

Name of patient	Signature	Date

Name of investigator consenting the patient	Signature	Date

## **APPENDIX L: CCS SAF SCALE**

The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale is determined by (S), symptoms attributable to AF; (A), association between symptoms (palpitations, dyspnea, dizziness/syncope, chest pain, weakness/fatigue) and documentation of AF or therapies for AF (ie, therapy associated symptoms); and (F), functional consequences of these symptoms on the patient’s daily function and quality of life.

The SAF class is then rated on a scale from 0 (asymptomatic) to 4 (severe impact of symptoms on QOL and activities of daily living). Table 1 shows how to determine the scale and Table 2 shows the scale definition.

Table 1: How to determine the CCS SAF Scale

<b>Step 1 - Symptoms</b>
<p>Identify the presence of the following symptoms:</p> <ul style="list-style-type: none"> <li>a. Palpitation</li> <li>b. Dyspnea</li> <li>c. Dizziness, presyncope or syncope</li> <li>d. Chest Pain</li> <li>e. Weakness or fatigue</li> </ul>
<b>Step 2 - Association</b>
<p>Is AF, when present, associated with the above-listed symptoms (a – e)?</p> <p>For example: Ascertain if any of the above symptoms are present during AF and likely caused by AF (as opposed to some other cause).</p>
<b>Step 3 - Functionality</b>
<p>Determine if the symptoms associated with AF (or the treatment of AF) affect the patient functionality (subjective quality of life)</p>

Table 2: CCS SAF Class Definition

Class 0
Asymptomatic with respect of AF
Class 1
<p>Symptoms attributable to AF have <b>minimal</b> effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Minimal and/or infrequent symptoms, or</li> <li>• Single episode of AF without syncope or heart failure</li> </ul>
Class 2
<p>Symptoms attributable to AF have a <b>minor</b> effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Mild awareness of symptoms in patients with persistent/permanent AF, or</li> <li>• Rare episodes (e.g. less than a few per year) in patients with paroxysmal or intermittent AF</li> </ul>
Class 3
<p>Symptoms attributable to AF have a moderate effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Moderate awareness of symptoms on most days in patients with persistent/permanent AF, or</li> <li>• More common episodes (e.g. more than every few months) or more severe Symptoms, or both, in patients with paroxysmal or intermittent AF.</li> </ul>
Class 4
<p>Symptoms attributable to AF have a severe effect on patient's general QOL.</p> <ul style="list-style-type: none"> <li>• Very unpleasant symptoms in patients with persistent/paroxysmal AF and/or</li> <li>• Frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF and/or</li> <li>• Syncope thought to be due to AF and/or</li> <li>• Congestive heart failure secondary to AF.</li> </ul>





**ST. JUDE MEDICAL**  
MORE CONTROL. LESS RISK.

## Note To File

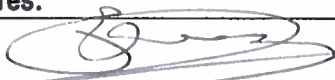

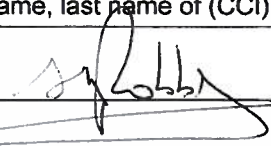
<b>Study Acronym:</b>	STAR AF II
<b>CPRB Number:</b>	AF-09-102-ID-AB
<b>Center/City/Country:</b>	NA
<b>Reference:</b>	Primary endpoint clarification

**Purpose of the Note-to-file (please detail below):**

In the clinicaltrials.gov website and in our methods paper, we have stated the primary endpoint as "freedom from documented AF episodes > 30 seconds at 18 months after one or two ablation procedures with/without antiarrhythmic medications". This was the identical primary endpoint used in the original STAR AF 1 pilot study (Verma et al, Eur Heart J 2010 Jun; 31(11):1344-56). The intent of this endpoint was to present the success rates after both 1 procedure and after 2 procedures separately as was done in the original STAR AF I pilot study. However, this is not entirely clear from the way the primary endpoint is stated. It may appear that our primary endpoint is the success rate after two procedures ("one or two" may imply "two").

Since our sample size calculation for the STAR AF II study was based on a single procedure success rate, the single procedure success rate with/without antiarrhythmics will be used as the principal primary endpoint. The success rate after two procedures will be provided as the first secondary endpoint.

This clarification is done prior to locking the database and prior to any data analysis. This "note to file" will be added to the trial protocol to clarify this point, and this clarification will also be added to the written statistical analysis plan. This note of clarification was also submitted to clinicaltrials.gov.

<b>Signatures:</b>	
	
<b>Dominik Elsen</b>	05/DEC/2013
Insert first name, last name of CPL	Date (dd/MMM/yyyy)
	
<b>Dr. Atul Verma</b>	04/DEC/2013
Insert title, first name, last name of (CCI) Investigator	Date (dd/MMM/yyyy)
	5 DEC 2013
<b>Hindrik Robbe</b>	
Insert first name, last name of VP Clinical affairs EMEA	Date (dd/MMM/yyyy)




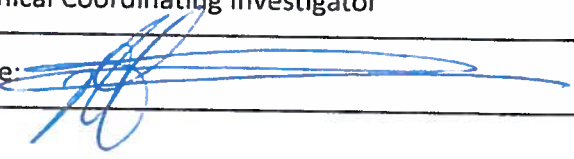
Note To File

<b>Project Name:</b>	STAR AF II
<b>Project Code:</b>	AF-09-102-ID-AB
<b>Center ID:</b>	NA
<b>Principal Investigator:</b>	NA
<b>Subject:</b>	Non-arrhythmic adverse event adjudication

**Purpose of the Note-to-file (please detail below):**

A blinded adjudication committee has been established consisting of Dr. Andrew Ha, Cardiac Electrophysiologist at the Toronoto General Hospital and Dr. Stephen Wilton, Cardiac Electrophysiologist at the Calgary Foothills Hospital for the STAR AF II trial.

The purpose will be for the committee to classify adverse clinical events as "not related", "probably related", or "definitely related" to the ablation procedure itself.

<b>Signatures (add as many fields as applicable):</b>	
Name: Dominik Elsen	Role: Clinical Project Leader
Date: December 18, 2013	Signature: 
Name: Dr. Atul Verma	Role: Clinical Coordinating Investigator
Date: December 18, 2013	Signature: 



Clinical Quality Records Approval

Sign Off page

Project	AF-09-102-ID-AB (Star AF II)
Clinical Quality Record	Clinical Statistics Analysis Plan (SAP)
Version	AF-09-102-ID-AB SAP- V1.0 13Jan2014

CLINICAL QUALITY RECORD ORIGINATOR

Title	Name	Signature	Date
Clinical Coordinating Investigator	Atul Verma		14 JAN 2014
Statistician	Ying (Emily) Zhang		14 Jan 2014

Does this version have an impact on Project (Y/N): if yes, describe	
Scope	N
Timelines	N
Resources	N
Costs	N
Patient Safety (Risk/Benefits)	N
Other Clinical Project Quality Records	N
Database Development	N
Data Entry	N
Statistics	N
Monitoring Activities	N
Training requirements	N

APPROVALS

Title	Name	Signature	Date
Senior Manager Statistics	Steven Ullery		14 JAN 2014
Clinical Project Leader	Dominik Elsen		14 JAN 2014



<b>Document Number</b>	<b>ID F060</b>	<b>Clinical Statistical Analysis Plan</b>
<b>Revision</b>	<b>1</b>	

<b>REVISION HISTORY</b>		
<b>Revision</b>	<b>Description of change</b>	<b>Originator</b>
1	FIRST RELEASE	Atul Verma /Ying ( Emily) Zhang

*This document is to be prepared by the statistics team with input from the project leader, Head of Statistics, clinical manager and safety manager.*

*The final version will be done before the analysis is performed.*

*If any update of a previous SAP has to be performed, the corresponding previous SAP will be updated. The new information will be highlighted.*

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## 1 Study Summary

<b>Study Name</b>	<b>STAR AF II</b>
<b>CPRB Number</b>	<b>AF-09-102-ID-AB</b>
<b>CRD Number</b>	<b>CRD_ 565</b>

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the analysis of the STAR AF II trial. This document will also include a detailed discussion of primary and secondary endpoints, and a listing of tables and figures.

### **1.1 Study Design and Study Flow Diagram**

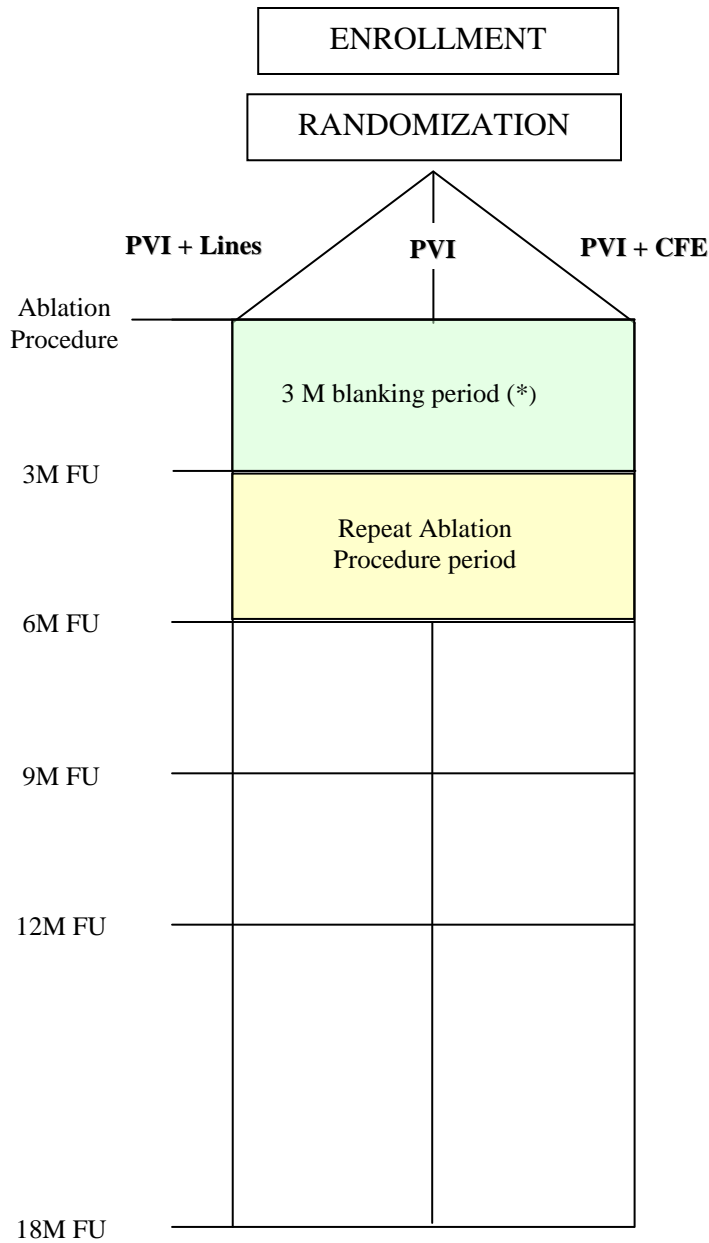
This investigation is a prospective, randomized, open-label, single-blind, multicenter, international, parallel study. The purpose of this study is to compare three strategies for the ablation of persistent AF.

Randomization shall be stratified by center, and all the patients are randomized in a 1:4:4 fashion to one of the investigation arms respectively:

- Pulmonary vein antrum isolation alone (PVI);
- Pulmonary vein antrum isolation plus ablation of complex fractionated electrograms (PVI+CFE);
- PVI plus empiric linear ablation (PVI+Lines).

The patient will participate in this investigation for approximately 18 months from enrollment to the last follow-up, with per protocol scheduled visits at 3months, 6 months, 9 months, 12 months and 18 months, see Figure 1. The patient may withdraw from the investigation at any time, for any reason.

**Figure 1: Study flow**



(\*) AF/AT/AFL recurrence during the blanking period will not be taken into account.

## **1.2 Primary Objective**

The primary objective of this investigation is to compare the efficacy of three different AF ablation strategies in patients with persistent AF targeting:

- Only the triggers of AF via PV antrum isolation (PVI) alone;
- A combination of the triggers plus the substrate of AF as defined by complex fractionated electrograms (PVI+CFE); and
- A combination of the triggers plus the substrate of AF by empiric linear ablation (PVI+Lines).

## **1.3 Secondary Objectives**

The secondary objectives of this investigation are to evaluate and compare:

- The safety and procedural characteristics of:
  - PVI alone versus
  - PVI+CFE versus
  - PVI+Lines.
- The quality of life between patients treated with:
  - PVI alone versus
  - PVI+CFE versus
  - PVI+Lines.

## **1.4 Inclusion Criteria**

The following inclusion criteria will be applied to all prospective candidates:

- Patients age is 18 years or greater;
- Patients undergoing a first-time ablation procedure for AF;
- Patients with persistent AF;
  - Persistent AF will be defined as a sustained episode lasting > 7 days and less than 3 years.
- Patients with symptomatic AF that is refractory to at least one antiarrhythmic medication;



- Symptomatic patients are those who have been aware of their AF at any time within the last 5 years prior to enrollment. Symptoms may include, but are not restricted to, palpitations, shortness of breath, chest pain, fatigue, left ventricular dysfunction, or other symptoms, or any combination of the above.
- At least one episode of persistent AF must have been documented by ECG, holter, loop recorder, telemetry, trans telephonic monitoring (TTM), or implantable device within last 2 years of enrollment in this investigation;
- Patients must be able and willing to provide written informed consent to participate in this investigation; and
- Patients must be willing and able to comply with all peri-ablation and follow-up requirements.

### **1.5 Exclusion Criteria**

Patients will be excluded from the study if they meet any of the following criteria:

- Patients with paroxysmal AF;
  - Paroxysmal AF will be defined as a sustained episode lasting < 7 days.
- Patients with long-standing persistent AF;
  - Long-standing persistent AF will be defined as a sustained episode lasting more than 3 years.
- Patients for whom cardioversion or sinus rhythm will never be attempted/pursued;
- Patients with AF felt to be secondary to an obvious reversible cause;
- Patients with contraindications to systemic anticoagulation with heparin or coumadin or a direct thrombin inhibitor;
- Patients with left atrial size  $\geq 60$  mm (2D echocardiography, parasternal long axis view); and
- Patients who are pregnant.
  - Pregnancy will be assessed by patients informing the physicians.

### **1.6 Study Population**

The **Intention-To-Treat (ITT)** population will include all patients who met the study inclusion/exclusion criteria, signed a patient informed consent, and had one of the three study ablation strategies performed. All the patients will be analyzed according to the randomized treatment strategy.

The **As Treated** population for primary endpoint analysis will include all patients who met the study inclusion/exclusion criteria, signed a patient informed consent, and who had one of the three study ablation strategies performed. The analysis for this population will be based on the treatment actually received during the first ablation strategy. For analysis of secondary endpoints after 2 ablations, the patient will be analyzed according to initial received ablation strategy as long as treatment received at second ablation was identical to the initial one. If not, this patient would be considered a major protocol deviation and will be excluded from analysis. These patients will be identified on a case-by-case basis by the Project Leader.

Primary endpoint analysis will be performed on both ITT and As Treated population. Unless otherwise specified, secondary endpoint analysis will be performed on the ITT population.

### **1.7 Primary Endpoint**

The primary endpoint will be the time to first recurrence of documented atrial fibrillation (AF) episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after one ablation procedure with or without the presence of antiarrhythmic medication.

There is a clarification on the primary endpoint. The primary endpoint listed on the initial version of clinicaltrials.gov and the methods paper in the American Heart Journal (Verma et al, Am Heart J 2012 Jul; 164(1):1-6) was stated as “freedom from documented AF episodes >30 seconds at 18 months after 1 or 2 ablation procedures with/without antiarrhythmic medications.” This was the identical primary endpoint used in the original STAR AF 1 pilot study (Verma et al, Eur Heart J 2010 Jun; 31(11):1344-56). The intent of this endpoint was to present the success rates after both 1 procedure and after 2 procedures separately as was done in the original STAR AF 1 pilot study. Since our sample size calculation for the STAR AF 2 study was based on a single procedure success rate (see sample size calculation section 3.1), the single procedure success rate with/without antiarrhythmics will be used as the principal primary endpoint. The success rate after 2 procedures will be provided as the first secondary endpoint.

### **1.8 Secondary endpoints**

1. Time to first recurrence of documented AF episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.

2. Time to first recurrence of any documented atrial arrhythmia (AF, atrial flutter AFL, or atrial tachycardia AT) episode > 30 seconds at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.
3. Time to first recurrence of documented AF/AFL/AT episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.
4. Time to first recurrence of documented AFL/AT episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after one ablation procedure with or without the presence of antiarrhythmic medication.
5. Time to first recurrence of documented AFL/AT episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.
6. Time to first recurrence of symptomatic AF > 30 seconds at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.
7. Time to first recurrence of symptomatic AF > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.
8. Time to first recurrence of any symptomatic atrial arrhythmia (AF/AFL/AT) episode > 30 seconds at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.
9. Time to first recurrence of any symptomatic atrial arrhythmia (AF/AFL/AT) episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.
10. Time to first recurrence of AF > 30 seconds documented or not at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.
11. Time to first recurrence of AF > 30 seconds documented or not after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.
12. Time to first recurrence of any atrial arrhythmia (AF/AFL/AT) episode > 30 seconds documented or not at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.

13. Time to first recurrence of any atrial arrhythmia (AF/AFL/AT) episode > 30 seconds documented or not after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures with or without the presence of antiarrhythmic medication.
14. Incidence of antiarrhythmic drug utilization
15. Improvement in AF burden by > 90% post ablation procedure
16. Incidence of repeat ablation procedures overall and between arms.
17. Incidence of peri-procedural complications, including stroke, PV stenosis, cardiac perforation, esophageal injury and death overall and between arms
18. Incidence of mortality
19. Mapping time, Procedure duration & Fluoroscopy time
20. Effect of each strategy on AF cycle length
21. Effect of each strategy on arrhythmia termination/regularization
22. Effect of acute termination of AF on long-term procedural outcome
23. Effect of achieving complete linear block on long term outcome in the linear ablation arm
24. Effect of achieving complete CFE ablation on long-term outcome in the CFE ablation arm
25. Effect of achieving complete PV isolation on long-term outcome in all arms;
26. Quality of life measurements at baseline and 6, 12 and 18 months post-ablation using the SF-36, EQ5D, and CCS SAF tools
27. Proportion of patients experiencing > 1 min, > 10 min, > 1 hour, > 24 hours AF post-ablation after one procedure with or without the presence of antiarrhythmic medication.
28. Proportion of patients experiencing > 1 min, > 10 min, > 1 hour, > 24 hours AF post-ablation after two procedures with or without the presence of antiarrhythmic medication.
29. Proportion of patients experiencing > 1 min, > 10 min, > 1 hour, > 24 hours AF/AFL/AT post-ablation after one procedure with or without the presence of antiarrhythmic medication.
30. Proportion of patients experiencing > 1 min, > 10 min, > 1 hour, > 24 hours AF/AFL/AT post-ablation after two procedures with or without the presence of antiarrhythmic medication.
31. Occurrence of non-AF atrial arrhythmia during the first ablation procedure
32. Occurrence of non-AF atrial arrhythmia during the second ablation procedure
33. Cost utility

Secondary endpoints #1 -#13 and #15-#26 are CIP specified endpoints, and the related analysis will be included in the SJM clinical final report. Secondary endpoints #14 and #27-#32 are defined mainly for manuscript, and this will not be included in the clinical final report.

In the CIP, the following secondary analyses were specified as secondary endpoints: Correlation of AF burden to symptoms and quality of life changes; relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome. These are all discussed in detail in section 3.2.5 “Other Pre-specified secondary analyses.”

## **1.9 Organizational Information**

### **1.9.1 Data Management**

The main data base is an RDC system. And the data management will be performed by the **Data Management Team** from the St. Jude Medical Clinical Department ID. The data management tool used will be **Oracle Clinical™ v 4.5**.

The TTM database has been collected, monitored and blindly adjudicated by a core laboratory (Vitaphone, Germany). The database monitors patient compliance with TTMs, interpretation of the TTM rhythm, and whether the TTM was a symptomatic or asymptomatic transmission. Five percent of all TTMs were independently, blindly adjudicated and cross-referenced by members of the study steering committee for quality assurance of the core laboratory.

All **adverse events** (AEs) defined according to ISO 14155 during the follow-up were collected for all patients. If an adverse event is documented at the patient’s last follow up visit (18 months), both the notification and follow-up information on the AE CRF were provided to the sponsor. Pre-existing cardiac conditions that require planned hospitalization were not to be considered as AE. In order to ensure that we collected all arrhythmia recurrences, these recurrences were classified as serious adverse events (SAEs) by protocol. All SAEs that were not arrhythmia recurrences were adjudicated by clinical event reviewers who were two blinded physicians not directly associated with the study that classified the SAEs and determined if they were procedure-related or not. If the first individual could not make an adequate determination with available documentation, it would be reviewed by the second individual and further source documentation would be requested as required.

### 1.9.2 Statistical Analysis

The statistical analysis and reporting is conducted by the *Statistician* from the St. Jude Medical Clinical Department ID. The statistical analyses will be performed using SAS™ software v 9.2 and NCSS 2007.

### 1.9.3 Interim Analysis

No interim analyses are planned.

### 1.9.4 Imputation

Imputation for quality of life questionnaire will be implemented per questionnaire guidelines. No imputation techniques will be used for other missing data.

### 1.9.5 Timings

The final data extract will be performed when all data is entered in the database, all DCFs are solved and the database has been cleaned, unless decided by the Clinical Project Leader.

### 1.9.6 Further Notes

- In case any **example** is used in this SAP, the numbers are fictitious and are only used to make a better presentation of the intended analyses.
- In case name of data sets or parameters are used in the SAS programs in this SAP, the names are fictitious and are only used to make a better presentation of the intended programs.
- All which is summarized under “**Other**” in the tables should be discussed in further detail below that table or in the appendix /addendum.

## 2 Results

### 2.1 Patient Disposition

The total number of participating centers + number of participating countries will also be stated, and a figure as Figure 2 representing the distribution of patients by center will be reported.

The number of patients screened, enrolled, randomized and completing the study will be included. A flow chart of patient disposition will be provided, (see example Figure 3).

The following dates will also be provided: date of first recruitment, date of last recruitment, date of final follow-up visit and date of database lock.

The number of patients that violated the inclusion/ exclusion criteria will be mentioned.

**Figure 2: Number of patients per center**

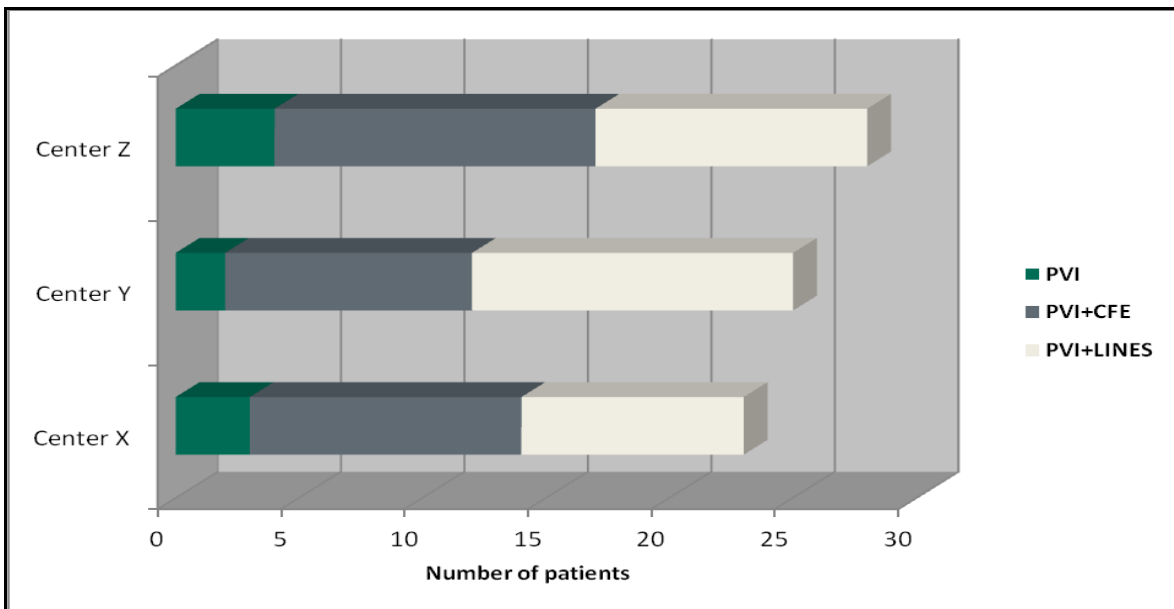
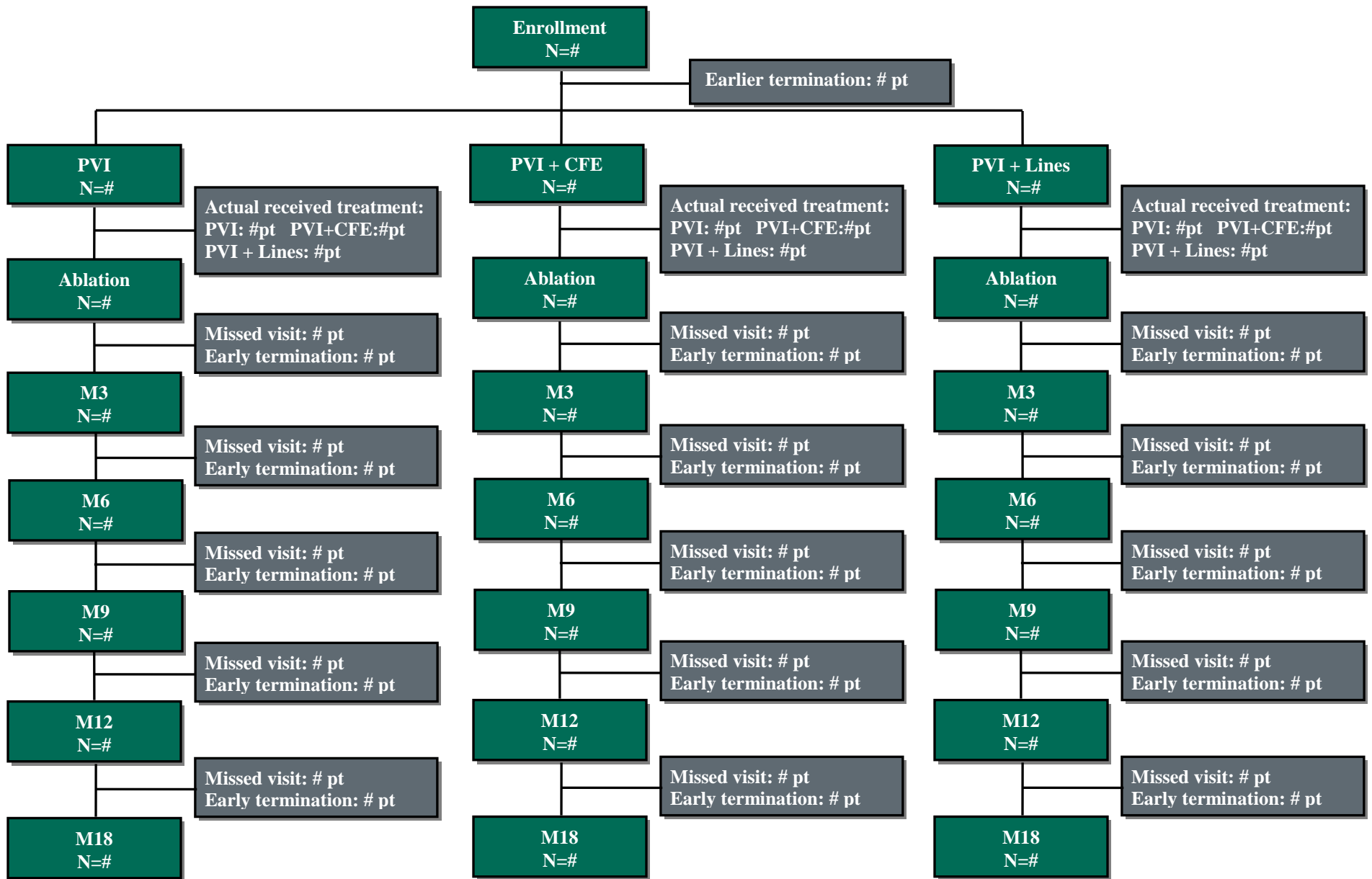


Figure 3: Disposition of patients





## 2.2 Baseline Demographics and Data

Demographics and baseline clinical criteria per study arm will be summarized using descriptive statistics. Data presented will include (but not be limited to): age, gender, duration of AF diagnosis, number of patients continuously in AF, number of patients not continuously in AF, average episode duration, number of episodes per month, number of cardioversions, co-morbid cardiac conditions, hypertension, diabetes, stroke/TIA, number of antiarrhythmics failed and which ones, NYHA and CCS SAF scores, CHADS and CHADSVASC scores, ejection fraction, and left atrial size. Table 1 gives an example for presenting the baseline data. The categorical data will be reported with the count and percentage. The number of non-missing values, mean, standard deviation, median and range will be reported for the continuous parameters.

**Table 1: Demographic data**

	Randomized group			
	PVI N=n1	PVI + CFE N=n2	PVI + Lines N=n3	Total N=n1+n2+n3
<b>Gender</b> (n / %)				
Female				
Male				
<b>Age</b> (years) <sup>1</sup>				
n				
Mean				
Std Dev				
Median				
Range				

## 2.3 TTM Compliance

Compliance with the TTMs refers to the patient's compliance in transmitting weekly TTM rhythm strips for arrhythmia monitoring during the 18 month follow-up. Compliance will be calculated as:

$$\frac{\text{the number of TTM transmissions received from the patient during the study}}{\text{the number of weeks in the study}} \times 100\%$$

<sup>1</sup> Age will be calculated by subtracting the date of the pre-intervention/baseline visit with the date of birth divided by 365.25 (because of the leap years).

## 2.4 Ablation Details (Initial procedure)

- Pre-procedure information:
  - Rhythm at onset of ablation, AF induction, use of isoproterenol and dose (if applicable) will be reported
- Ablation information:
  - For the PV isolation, whether PVI was performed and the success rate of achieving complete PV isolation for all patients will be reported. For instances where PV isolation is not achieved, the number and names of the non-isolated PVs will be specified.
  - For the CFE ablation, the location of CFE sites and whether CFE ablation was performed will be reported. Completion of ablation of all CFE sites will also be reported. Location of ablated and non-ablated CFE sites will be specified.
  - For the linear ablation, whether linear ablation was performed and the completion rate of each of the mitral and roof lines will be reported. The achievement of block across each line will be detailed.
  - Baseline AF cycle length and changes in AF cycle length after PVI, CFE or linear ablation will be reported. Rates of termination of AF to sinus or another arrhythmia after each of PVI, CFE and linear ablation will also be reported. The type of arrhythmia to which AF terminated will also be specified.
  - Occurrence of other arrhythmias during the ablation and whether they were targeted or not will be detailed (will include details of whether AFL, AT or SVT seen and/or ablated).
  - Whether right atrial flutter line (see Ablation CRF G1.1.3) was performed will be detailed.
  - Procedure time
  - Fluoroscopy time

**Table 2: Ablation success rate**

	Definition
Number of PVs	Ablation CFE, section D1
Which PVs were successfully isolated?	Ablation CRF, section D3
Successful isolation of all PVs	If Ablation CRF section D3 has same amount of PVs as section D1, or has more PVI than section D1, then considered to have isolated all PVs.

	Definition
Location of CFE sites	Ablation CRF, section E2
Successful ablation of CFE sites	Ablation CRF section E3 is 'Yes'; or if E3 is "No" then response to E3.1 is "AF Terminated"
CFE sites not ablated	Ablation CRF, section E4
Success of roof line block	If Ablation CRF section F2 is 'Yes' then if F2.1 is 'Yes' too;
Success of mitral line block	If Ablation CRF section F4 is 'Yes' then if F4.1 is 'Yes' as well; Or F4.1.1 is 'Yes' then if F4.1.1.1 is 'Yes' as well.
Success of linear ablation	Combination of roof line block and mitral line block

### 2.5 Crossover Details (initial procedure)

A patient randomized to the PVI arm will be considered to be a crossover if CFE and/or left atrial roof/mitral linear ablation were performed. A patient randomized to the PVI+CFE arm will be considered to be a crossover if left atrial roof/mitral linear ablation was performed. If a patient in the PVI+CFE arm had the PVI completed, but AF was subsequently non-inducible such that CFE could not be performed, the patient would NOT be considered a crossover since this is an accepted part of this strategy. A patient randomized to PVI+Lines would be considered a crossover if any CFE ablation was done or if PVI alone was done without lines. Performing a line other than a mitral and/or left atrial roof line in any arm (a right atrial cavotricuspid isthmus line, for example), will not be considered a crossover.

**Table 3: Crossover information for each arm (initial procedure)**

Received treatment	Randomized treatment							
	PVI		PVI + CFE		PVI + LINES		Total	
	N=n1		N=n2		N=n3		N=n1+n2+n3	
	n	%	n	%	n	%	n	%
PVI								
PVI + CFE								
PVI + LINES								
PVI + CFE +LINES								
Other								

## **2.6 Repeat Ablation Details**

The number of patients receiving 2 or more ablations and the number of ablations per patient will be detailed overall and by each treatment arm. The time window for repeat ablation(s) will be specified for 0-3 months, 3-6 months, 6-9 months, 9-12 months, and 12-18 months for the total population and for each treatment arm. Similar information as section 2.5, if applicable, will be reported for the repeated ablation procedure.

The protocol specified that the identical randomized strategy must be used for the second left atrial ablation procedure as for the first. If a crossover occurred between the first and second ablation procedures, the patient will be considered a crossover for any of the endpoint analysis measured after two ablation procedures but not for the ones measured after one ablation procedure analyses. The same crossover rules specified in section 2.5 for the initial procedure shall apply to defining crossovers between the first and second procedures.

Details on the third or more procedures will also be provided where possible. Since the primary and secondary endpoints only look at single and dual procedure success rates, any patient receiving a third or more left atrial ablation procedure will automatically be considered as a “failure” after both 1 and 2 procedures. There were no protocol specifications for what type of ablation could be performed after the second procedure.

## **2.7 Medications**

Patient’s status regarding cardiac medications will be reported at each time point (3, 6, 9, 12, and 18 months) for the overall study and for each study arm. Only class I and class III antiarrhythmics will be defined as “antiarrhythmics.” Cardiac glycosides, calcium channel blockers, and non-sotalol beta-blockers will not be considered as antiarrhythmics. Patients off antiarrhythmics at the final follow-up will be considered as “off” antiarrhythmics whereas patients who continue to be on antiarrhythmics at final follow-up will be considered as “on” antiarrhythmics. Further details are specified in section 3.2.2.

## **2.8 Imaging data**

Other data to be presented will include echocardiographic data (ejection fraction, left atrial size, left ventricular hypertrophy, and significant valvular heart disease). CT and MRI data will also be presented where available, especially with regards to pulmonary vein stenosis.

## **2.9 Adverse Events and Deaths**

**Adverse events** defined according to ISO 14155 during the follow-up must be collected for all patients. If an adverse event is documented at the patient's last follow up visit (18 months), both the notification and follow-up information on the AE CRF are to be provided to the sponsor. Pre-existing cardiac conditions that require planned hospitalization are not to be considered as AE.

All adverse events will be reported. Arrhythmia recurrence was considered an adverse event by the protocol to ensure that all recurrences were documented. Arrhythmia recurrences will be reported separately in the outcomes (section 2.9) and will not be reported as adverse events in the study publication. Adverse events will be extracted from the adverse event CRFs and will be listed overall and by study group. All adverse events will be independently adjudicated by clinical event reviewers who are two blinded physicians not directly associated with the study (see section 1.9.1) that classified the SAEs according to seriousness and determined if they were procedure-related or not. A serious adverse event is defined as one causing death, or one that is life-threatening, or causes permanent disability or prolongation of hospitalization, or if it is classified as serious by the clinical event reviewers.

All deaths will be detailed including the cause (where possible) and whether it was study-related or not. Narratives for all deaths will be written.

**Table 4: Adverse events: global overview**

	Randomized treatment							
	PVI		PVI + CFE		PVI + LINES		Total	
	N=n1		N=n2		N=n3		N=n1+n2+n3	
	n	%	n	%	n	%	n	%
Total number of adverse events documented								
Number of pts with at least 1 adverse event document								

**Table 5: Adverse events: categories**

	Randomized treatment							
	PVI		PVI + CFE		PVI + LINES		Total	
	N=n1		N=n2		N=n3		N=n1+n2+n3	
	n	%	n	%	n	%	n	%
AEs								
Number of pts with at least 1 AE								
ADEs								
Number of pts with at least 1 ADE								
SAEs								
Number of pts with at least 1 SAE								
Number of SADEs								
Number of pts with at least 1 SADE								

**Table 6: Death - overview**

	Randomized treatment							
	PVI		PVI + CFE		PVI + LINES		Total	
	N=n1		N=n2		N=n3		N=n1+n2+n3	
	n	%	n	%	n	%	n	%
Deaths								
Study-related deaths								

**2.10 Early terminations**

All reasons and time window for the early termination will be reported and included in the study flow (see section 2.1 for details).

**2.11 Deviations**

For patients with protocol deviations, the number and type of deviation will be listed.

**Descriptive statistics for other parameters requested by CPL will be reported in the addendum.**

### 3 Statistical analysis

#### 3.1 Primary endpoint

##### 3.1.1 Sample size

The sample size calculation is based on the primary endpoint time to first recurrence of AF > 30 seconds after one procedure with or without antiarrhythmic medications. Based on the STAR AF 1 pilot study, the expected freedom from AF in the PVI+CFE group was 75% and the freedom from AF in the PVI alone group was 45% (Verma et al, Eur Heart J 2010). The STAR AF 1 study did not include an arm for PVI+Lines so the one procedure success rate was estimated from the literature at 60%. A one-sided log rank test at 2.5% significant level was used for sample size calculation.

In order to test if the PVI+CFE strategy is superior to the PVI+Lines strategy and the PVI strategy, a total of 468 patients is needed to maintain a power of 90% at a significance level of 5% (two sided), with a randomization ratio of 1:4:4 (PVI: PVI+CFE: PVI+Lines). It is required to have at least 52 patients in the PVI group, 208 each in PVI+CFE and PVI+Lines groups in the final analysis.

Taking into account a dropout rate of 15%, a total of 549 patients (61 in PVI group, 244 each in PVI+CFE group and PVI+Lines group) are required to be recruited.

##### 3.1.2 Hypothesis

The combined PVI+CFE approach will be superior to both the PVI + Lines and PVI groups in terms of time to first recurrence of AF > 30 seconds at 18 months after one ablation procedure.

$$H_0 : S_{COM} \leq S_{Line} \quad vs \quad H_1 : S_{COM} > S_{Line}$$

$$H_0 : S_{COM} \leq S_{PVI} \quad vs \quad H_1 : S_{COM} > S_{PVI}$$

Where  $S_{COM}$  is the survival rate (time to first recurrence of AF > 30 seconds) at 18 months after one ablations in PVI+CFE group;  $S_{Line}$  is the survival rate (time to first recurrence of AF > 30 seconds) at 18 months after one ablation in the PVI+Lines group;  $S_{PVI}$  is the survival rate (time to first recurrence of AF > 30 seconds) at 18 month after one ablation in the PVI group.



### 3.1.3 Population

Primary endpoint analysis will be performed on both ITT and As Treated population. The number of patients in each of the ITT and As Treated populations will be specified. A listing of the As Treated study population and As Treated population in each arm will be provided and the reasons for exclusion of patients from the As Treated population will also be detailed.

### 3.1.4 Analysis method for primary endpoint

A documented AF episode >30 seconds is defined as outlined in Table 7 and Figure 4. No episode of AF occurring within the three months blanking period post-initial ablation will be counted towards the primary endpoint as per the clinical investigation plan (CIP).

An episode of AF will be considered part of this primary endpoint if it is greater than 30 seconds and is documented by any one of ECG, telemetry, Holter, or transtelephonic monitor (TTM). Specifically for the TTM documentation, the duration of the TTM recording used in this study was 30 seconds; therefore, if more than one TTM with AF occurs anytime during the follow-up period, the patient will be considered to have met the requirement of a recurrence > 30 seconds. Alternatively, an episode of AF will be counted as part of the primary endpoint if the duration of the documented episode is specified as longer than 30 seconds according to the "Follow-up" clinical reporting form (CRF) section C (table C1.1, columns 4-6), or section F (table F1.1, columns 4 and 5). The time to recurrence will be calculated as the time to the first documented AF episode > 30 seconds according to the "Follow-up" CRF, or in the case where the only documented episodes are 2 or more TTMs, then the time to the first TTM recurrence will be used.

If a repeat left atrial ablation procedure is performed prior to any documented AF episode, then the date of this ablation will be used as the time to recurrence. If a patient undergoes a repeat ablation during which there is no entry into the left atrium, then this ablation procedure will not be counted as a second ablation procedure (e.g. right atrial flutter ablation with cavotricuspid isthmus ablation alone and no entry into left atrium).

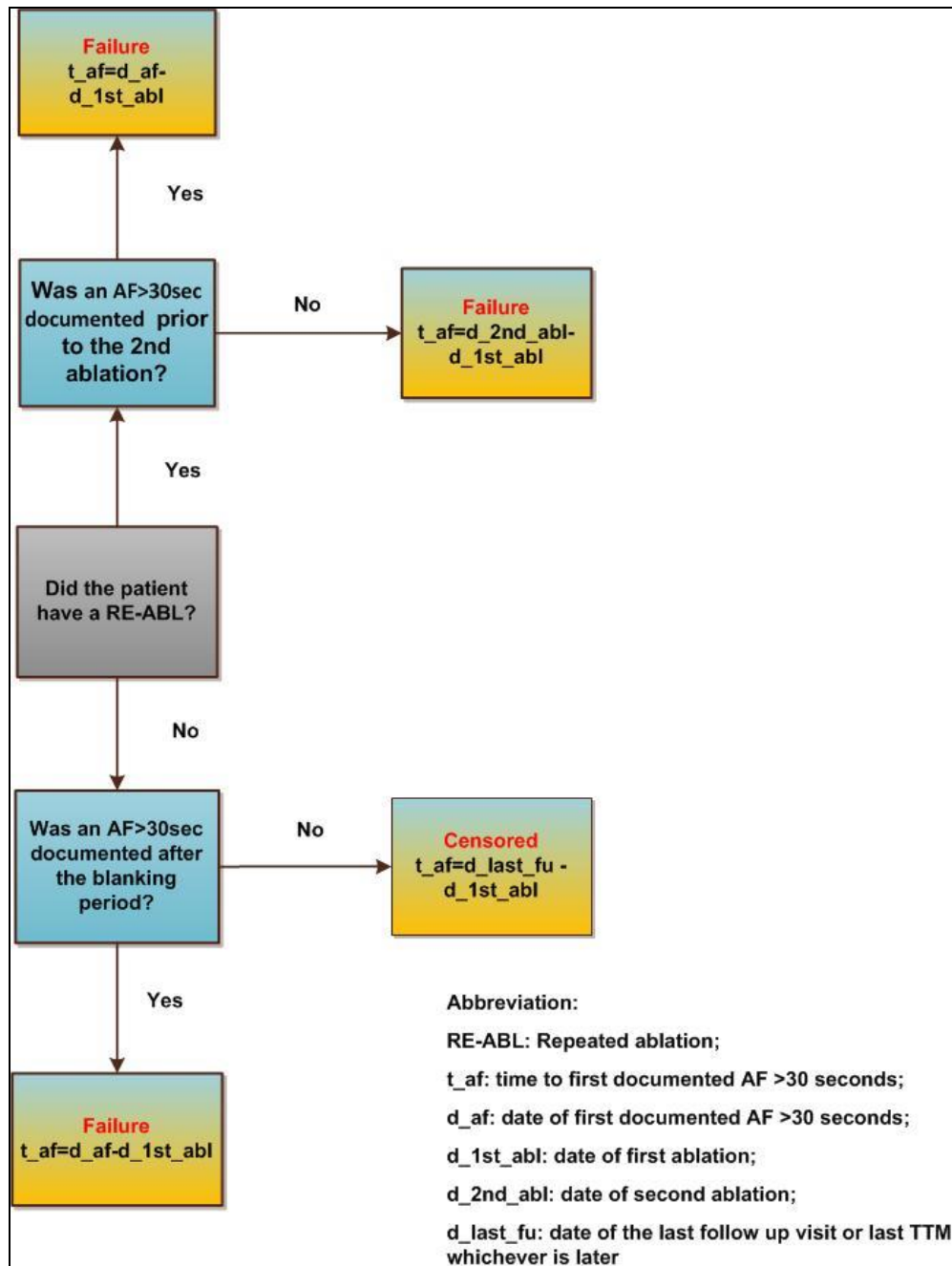
The TTM duration in this study is only 30 seconds, therefore if a patient only has 1 or no AF recorded by TTM after the 3 months blanking period, has no other documented recurrences, and no repeated left atrial ablation, then this patient will be considered to be 'censored' for the primary endpoint. For all patients who are censored for the primary endpoint, the date of the event will be the last follow up visit date or last TTM recording date, whichever comes later.

In case that a patient has terminated the study within blanking period (3 months post first ablation), this subject will be considered as a dropout and be excluded from the analysis.

**Table 7: Definition for time to first documented AF recurrence > 30 seconds post one ablation**

Event (Failure)	<p>First documented AF &gt; 30 seconds after 3 month blanking period post initial procedure</p> <p>OR</p> <p>More than one TTM with AF anytime during follow-up after 3 month blanking period post initial procedure</p> <p>OR</p> <p>Any repeat left atrial ablation procedure</p>
Date of the event	<p><b>For “failure”</b> - the date of the first documented AF &gt; 30 seconds or TTM after 3 months post initial procedure or repeat left atrial ablation, whichever comes first;</p> <p><b>For “censored”</b> - the last follow up visit date or last TTM recording date, whichever comes later;</p>

Figure 4: Calculation for time to first documented AF recurrence > 30 seconds post one ablation



The testing for each hypothesis will be performed using the log-rank test, and with the assist of Kaplan–Meier curves, a two sided p value smaller than 5% (or one sided smaller than 2.5%) will be considered to be significant. Below is an example for the SAS coding:

```

/*Log rank test for PVI+CFE vs PVI+Lines*/
proc lifetest data=crdata.enpt;
time tt_af*cens_af(0);
strata treatment;
where treatment in ('PVI + CFE', 'PVI + LINES');
run;

```

For any baseline demographic factor or factors of interest, its impact on the primary endpoint can be assessed. For this purpose, a Cox proportional regression model with treatment and above baseline factors will be used. Proportionality of the cox model will be checked as well. In case the proportionality assumption is violated for a certain covariate, further analysis will be performed by adding the interaction of time and this covariate. Or other survival models may be used if deemed more appropriate.

```

data temp;
set crdata.enpt;
if treatment in ('PVI') then grp_num=1;
if treatment in ('PVI + CFE') then grp_num=2;
if treatment in ('PVI + LINES') then grp_num=3;
run;

```

```

/*Cox regression */
proc phreg data=temp;
class grp_num(ref='3') factor1 factor2 factor3;
model tt_af*cens_af(0)=factor1 factor2 factor3 factor4 grp_num/ rl
ties=Efron;
run;

```

### **3.2 Secondary endpoints**

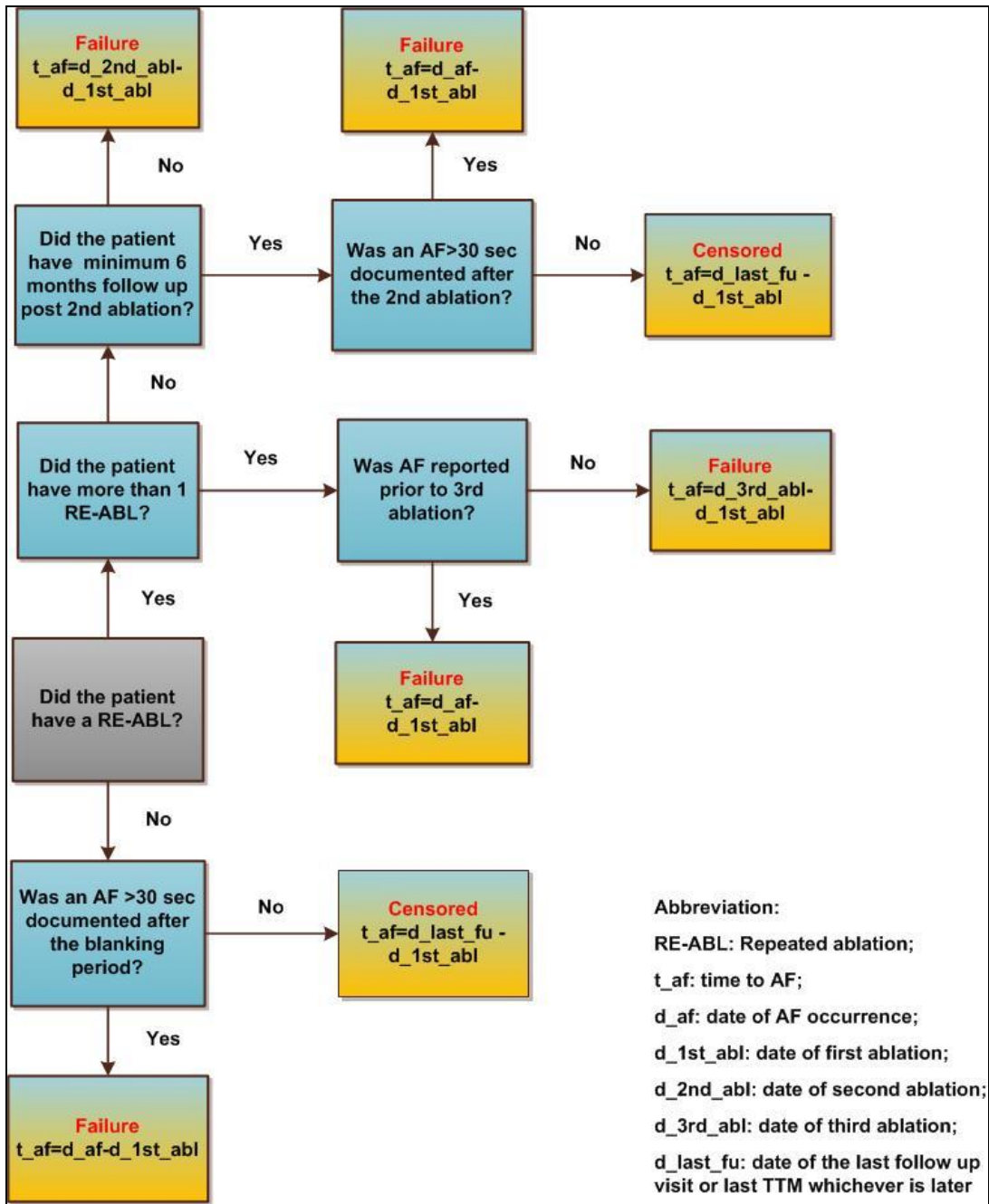
#### **3.2.1 Time to event secondary endpoints**

Secondary endpoints 1 - 13 are outlined in detail in this section. Survival analysis will be performed using the log rank test together with Kaplan–Meier curves among the three arms. And in case it is found to be significant, then appropriate post hoc analysis can be performed. If appropriate, multivariate survival analysis will be performed using same method as for the primary endpoint.

**1. Time to first recurrence of documented AF episode > 30 seconds after the initial three months blanking period until the end of study follow-up (18 months) after two ablation procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication**

- In case a patient has no repeated left atrial ablation, the event and the date of the event are defined the same as for the primary endpoint.
- If a patient undergoes a repeat ablation during which there is no entry into the left atrium, then this ablation procedure will not be counted as a second ablation procedure (e.g. right atrial flutter ablation with cavotricuspid isthmus ablation alone and no entry into left atrium)
- In case a patient has a second left atrial ablation procedure and has a minimum 6 months follow up afterwards, then any AF recurrence prior to this repeat ablation will not be considered as an event. The first documented AF > 30 sec after the repeat ablation or the occurrence of a third repeat left atrial ablation procedure will be considered as the failure event. There will be no blanking period after the second ablation procedure.
- If a patient has less than 6 months follow up after the second repeated left atrial ablation, the patient will be considered to be a failure, and the date of the second left atrial ablation will be the date of the event.
- This secondary analysis will be performed on both ITT and As Treated population.

Figure 5: Calculation for time to first documented AF recurrence > 30 seconds post one / two ablations



**Table 8: Definition for time to first documented AF recurrence > 30 seconds post two ablation procedures**

Event (Failure)	<p><b>Patient without a repeat left atrial ablation:</b>  First documented AF &gt; 30 seconds after 3 month blanking period post initial procedure  OR  More than one TTM with AF anytime during follow-up after 3 month blanking period post initial procedure</p> <p><b>Patient with a repeat left atrial ablation:</b>  First documented AF &gt; 30 seconds post repeat left atrial ablation  OR  More than one TTM with AF anytime during follow-up after the second procedure  OR  A third left atrial ablation procedure  OR  The second left atrial ablation if less than 6 months follow-up after that ablation</p>
Date of the event	<p><b>For “failure” – Patient without repeat left atrial ablation:</b>  the date of the first documented AF &gt; 30 seconds/TTM after 3 months post initial procedure;</p> <p><b>For “failure” – Patient with repeat left atrial ablation:</b>  the date of the first documented AF &gt; 30 seconds/TTM after second left atrial ablation or date of the third left atrial ablation, or date of the second ablation if less than 6 months follow-up after that ablation, whichever comes first;</p> <p><b>For “censored”</b> - the last follow up visit date or last TTM recording date, which comes later;</p>

**2. Time to first recurrence of any documented atrial arrhythmia (AF, atrial flutter AFL, or atrial tachycardia AT) episode > 30 seconds at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.**

- This endpoint is defined similar to the primary endpoint, but the event includes the recurrence of any atrial arrhythmia (AF, AFL or AT) after one procedure
- Any repeat ablation (including right atrial) will be considered as a redo for the AFL/AT related endpoint
- For differentiation of AF from AFL or AT recurrences for the secondary endpoints, the determination will be made from the “Follow-up” CRF, table C1.1, column 2 or from table F1.1, column 2, or from the adjudicated TTM interpretation from the core laboratory.
- This secondary analysis will be performed on both ITT and As Treated population.

**Table 9: Calculation for time to first documented AF/AFL/AT recurrence >30 sec post one ablation**

Event (Failure)	First documented AF/AFL/AT > 30 seconds after 3 month blanking period post initial procedure OR More than one TTM with AF/AFL/AT any time during follow-up after 3 month blanking period OR Any repeat procedure
Date of the event	<b>For “failure”</b> - the date of the first documented AF/AFL/AT > 30 seconds/TTM after 3 months post initial procedure or repeat ablation, whichever comes first; <b>For “censored”</b> - the last follow up visit date or last TTM recording date, which comes later;

**3. Time to first recurrence of documented AF/AFL/AT episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication.**

- This endpoint is defined similar to the first secondary endpoint in this section, but the event includes the recurrence of any atrial arrhythmia (AF, AFL or AT) after two procedures
- Any repeat ablation will be considered as a redo for AFL/AT related endpoint



- For differentiation of AF from AFL or AT recurrences for the secondary endpoints, the determination will be made from the “Follow-up” CRF, table C1.1, column 2 or from table F1.1, column 2, or from the adjudicated TTM interpretation from the core laboratory.
- This secondary analysis will be performed on both ITT and As Treated population.

**Table 10: Calculation for time to first documented AF/AFL/AT recurrence >30sec post two ablation procedures**

Event (Failure)	<p><b>Patient without repeat ablation:</b>  First documented AF/AFL/AT &gt; 30 seconds after 3 month blanking period post initial procedure  OR  More than one TTM with AF/AFL/AT any time during follow-up after 3 month blanking period</p> <p><b>Patient with repeat ablation:</b>  First documented AF/AFL/AT &gt; 30 seconds post repeat left atrial ablation  OR  More than one TTM with AF/AFL/AT anytime during follow-up after the second procedure  OR  third left atrial ablation procedure  OR  The second left atrial ablation if less than 6 months follow-up after that ablation</p>
Date of the event	<p><b>For “failure” – Patient without repeated ablation:</b>  the date of the first documented AF &gt; 30 seconds/TTM after 3 months post initial procedure;</p> <p><b>For “failure” – Patient with repeated ablation:</b>  the date of the first documented AF &gt; 30 seconds/TTM after second left atrial ablation or date of the third ablation, or date of the second ablation if less than 6 months follow-up after that ablation, whichever comes first;</p> <p><b>For “censored”</b> - the last follow up visit date or last TTM recording date, which comes later;</p>

**4. Time to first recurrence of documented AFL/AT episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after one ablation procedure with or without the presence of antiarrhythmic medication.**

- This endpoint is defined similar to secondary endpoint #2 in this section, except the event will only include AFL and AT recurrences and exclude AF recurrences
- Any repeat ablation (including right atrial) will be considered as a redo for the AFL/AT related endpoint

**5. Time to first recurrence of documented AFL/AT episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication.**

- This endpoint is defined similar to secondary endpoint #3 in this section, except the event will only include AFL and AT recurrences and exclude AF recurrences
- Any repeat ablation (including right atrial) will be considered as a redo for the AFL/AT related endpoint

**6. Time to first recurrence of symptomatic AF > 30 seconds at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.**

- This endpoint is defined similar to the primary endpoint, but only symptomatic AF recurrence will be taken into account.
- A recurrence > 30 seconds will be considered symptomatic if it is specified as being symptomatic in section C of “Follow-up” CRF (table C1.1, column 3) or section F (table F1.1, column 3), or from the “symptomatic” label on TTM. All other recurrences will be considered “asymptomatic.” The SAP acknowledges that if multiple TTMs are transmitted simultaneously by a patient, they all will carry the same “symptomatic” or “asymptomatic” label even if some were symptomatic and some were not. This will result in an anticipated under- or over-estimation in the number of symptomatic episodes assessed by TTM.

**7. Time to first recurrence of symptomatic AF > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation**

***procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication.***

- This endpoint is defined similar to first secondary endpoint in this section, but only symptomatic AF recurrence will be taken into account.
- Please see definition of “symptomatic” in secondary endpoint #6 in this section above.

**8. *Time to first recurrence of any symptomatic atrial arrhythmia (AF/AFL/AT) episode > 30 seconds at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.***

- This endpoint is defined similar to secondary endpoint #2 in this section, but only symptomatic AF/AFL/AT recurrence will be taken into account.
- Please see definition of “symptomatic” in secondary endpoint #6 in this section above.

**9. *Time to first recurrence of any symptomatic atrial arrhythmia (AF/AFL/AT) episode > 30 seconds after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication.***

- This endpoint is defined similar to secondary endpoint #3 in this section, but only symptomatic AF/AFL/AT recurrence will be taken into account.
- Please see definition of “symptomatic” in secondary endpoint #6 in this section above

**10. *Time to first recurrence of AF > 30 seconds documented or not at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.***

- This endpoint is defined similar to the primary endpoint, except it will take all the AF recurrence, documented or not, into account.
- Determination of documentation will be made from section C of “Follow-up” CRF (table C1.1, columns 4-6)

**11. *Time to first recurrence of AF > 30 seconds documented or not after the initial three month blanking period until the end of study follow-up (18 months) after two ablation***

***procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication.***

- This endpoint is similar to the first secondary endpoint in this section, except it will take all the AF recurrence, documented or not, into account.
- Please see definition of “documented” in secondary endpoint #10 in this section above.

***12. Time to first recurrence of any atrial arrhythmia (AF/AFL/AT) episode > 30 seconds documented or not at 18 months after one ablation procedure with or without the presence of antiarrhythmic medication.***

- This endpoint is defined similar to secondary endpoint #2 in this section, except it will take all the AF/AFL/AT recurrence into account, regardless of whether it is documented or not
- Please see definition of “documented” in secondary endpoint #10 in this section above.

***13. Time to first recurrence of any atrial arrhythmia (AF/AFL/AT) episode > 30 seconds documented or not after the initial three month blanking period until the end of study follow-up (18 months) after two ablation procedures (if there is a second procedure) with or without the presence of antiarrhythmic medication.***

- This endpoint is similar to secondary endpoint #3 in this section, except it will take all the AF/AFL/AT recurrence into account, regardless of whether it is documented or not.
- Please see definition of “documented” in secondary endpoint #10 in this section above.

***14. Effect of acute termination of AF to long-term procedural outcome***

Acute AF termination is defined in Table 11. Survival analysis, log rank test, will be used to assess the impact of acute termination of AF on long-term procedural outcome, with the aid of Kaplan-Meier curve.

The long term procedural outcome will include the primary endpoint and the secondary endpoints #1-3 in this section: ‘Freedom from documented AF episodes > 30 seconds at 18 months after two procedures with/without antiarrhythmic medications’ and ‘Freedom from any AF/AFL/AT > 30 seconds at 18 months with/without antiarrhythmic medications” after both one and after two procedures.’

**Table 11: Defining AF Termination**

Treatment	Definition
PVI	If Ablation CRF section D4 is 'Yes'
PVI + CFE	Either Ablation CRF section D4 or section E5 is 'Yes';
PVI + LINE	Either Ablation CRF section D4 or section F6 is 'Yes' ;

**15. Effect of achieving complete linear block on long term outcome in the linear ablation arm;**

In the patients who received PVI+Lines, whether or not they achieved complete linear block of both lines could impact long-term outcome. Patients who had block of both lines will be identified by an answer of "Yes" to both F2.1 and F4.1 on the "Ablation" CRF. Patients who do not have an answer of "Yes" to both questions will be considered to not have complete linear block achieved. We will only analyse those patients who had a successful PV isolation prior to creating lines to as to isolate the effect of incomplete lines by themselves. The log rank test will be used to assess the impact of complete linear block on long-term procedural outcome, with the aid of Kaplan-Meier curve.

The long term procedural outcome will include primary endpoint as well as the secondary endpoints #1-3 in this section: 'Freedom from documented AF episodes > 30 seconds at 18 months after two procedures with/without antiarrhythmic medications' as well as the other secondary endpoints of "Freedom from any AF/AFL/AT > 30 seconds at 18 months with/without antiarrhythmic medications" after both one and after two procedures.

Analysis will be only performed in the As Treated population for those who received linear ablation.

**16. Effect of achieving complete CFE ablation on long-term outcome in the CFE ablation arm;**

In the patients who received PVI+CFE, whether or not they achieved complete ablation of CFE could impact long-term outcome. Patients who had complete CFE ablation will be identified by an answer of "Yes" to E3 on the "Ablation" CRF, or if they answered "No" to E3 but the reason for not completing CFE ablation was because "AF Terminated" as an answer to E3.1. Other patients in this arm will be considered to have had incomplete CFE ablation. We will only analyse those patients who had a successful PV isolation prior to creating lines to as to isolate the effect of incomplete lines by themselves. The patients who are not in AF prior to CFE ablation and are

impossible to induce the AF will be excluded from this analysis as well. The log rank test will be used to assess the impact of complete CFE mapping on long-term procedural outcome, with the aid of Kaplan-Meier curve.

The long term procedural outcome will include primary endpoint as well as secondary endpoints #1-3 in this section: 'Freedom from documented AF episodes > 30 seconds at 18 months after two procedures with/without antiarrhythmic medications' as well as the other secondary endpoints of "Freedom from any AF/AFL/AT > 30 seconds at 18 months with/without antiarrhythmic medications" after both one and after two procedures.

Analysis will be only performed in the As Treated population for those who received CFE ablation.

### ***17. Effect of achieving complete PV isolation on long-term outcome in all arms;***

In the patients who received any of the ablation strategies, whether or not they achieved complete isolation of all PVs could impact long-term outcome. If Ablation CRF section D3 has same amount of PVs as section D1, or has more PVs than section D1, then the patient will be considered to have had all PVs isolated. The log rank test will be used to assess the impact of complete PVI isolation on long-term procedural outcome, with the aid of Kaplan-Meier curve. Kaplan-Meier curves of complete vs incomplete PVI will also be presented with the sub-stratification of treatment group. Post hoc analysis can be done in case the survival plot shows a trend that there is difference between the treatments.

The long term procedural outcome will include primary endpoint as well as the first secondary endpoint 'Freedom from documented AF episodes > 30 seconds at 18 months after two procedures with/without antiarrhythmic medications' as well as the other secondary endpoints of "Freedom from any AF/AFL/AT > 30 seconds at 18 months with/without antiarrhythmic medications" after both one and after two procedures.

Analysis will be only performed in the As Treated population.

### **3.2.2 Categorical secondary endpoints**

The number of occurrence and proportion will be reported per randomized arm for all the categorical secondary endpoints.

#### ***1. Incidence of antiarrhythmic drug utilization***

For determination of whether the patient is on or off antiarrhythmic drug therapy, antiarrhythmic drugs will be defined as class I or class III antiarrhythmics. Cardiac glycosides, calcium channel blockers and non-sotalol beta-blockers will not be included as antiarrhythmics. Patients will be defined as “off” antiarrhythmics if they are not on an antiarrhythmic at the time of their final follow-up. Incidence of antiarrhythmic drug usage at 18 months will be compared among the randomized groups using chi-square test or Fisher exact test. Proportions of patients on antiarrhythmics can be reported at each time point for the overall study and for each study arm. Bar plots will be used to present the antiarrhythmic drug utilization across time and treatment. In case any trends for the evolution is presented in the plot, the post hoc analysis, using the GEE (Generalized Estimation Equation) model or other model for repeated measurements, can be performed in order to assess the treatment effect on antiarrhythmic medication utilization over time.

## **2. Incidence of peri-procedural complications**

The following specified complications will be considered as peri-procedural complications. Peri-procedural complication is related to any ablation procedure.

- Stroke or TIA ( $\leq 30$  days)
- Symptomatic PV stenosis (any time during the study)
- Cardiac perforation without tamponade ( $\leq 48$  hours)
- Cardiac tamponade ( $\leq 48$  hours)
- Vascular complications : haematoma ( $\leq 7$  days)
- Pseudoaneurysm ( $\leq 30$  days)
- Bleed requiring transfusion ( $\leq 7$  days)
- Atrio-esophageal fistula (any time during the study)
- Severe esophageal injury ( $\leq 30$  days)
- Death (Due to one of the above complications within timeframe listed)

Chi-square test will be used for the comparison of complications between the treatment groups. In case more than 25% of the cells count less than 5, fisher exact test will be used instead. In case a significant difference is found among the treatment, further post hoc analysis, such as multivariate logistic regression, can be performed.

```
proc freq data=crdata.ae;  
table treatment*peri_ae/cmh chisq fisher;  
run;
```

### 3. Effect of each strategy on AF cycle length

Initial AF cycle length and final AF cycle length will be reported for all patients who were in AF during their procedure. Patients will be further classified to 'AF cycle length prolonged' and 'AF cycle length not prolonged' based on the difference between the final and initial AF cycle length. The proportion for each class will be reported per treatment group, and Chi-square test or Fisher exact will be used for comparison.

The difference between the final and initial AF cycle length will be compared among the three ablation strategies. One way ANOVA will be used for the comparison among the groups. In case the assumption for ANOVA is violated, then the equivalent non-parametric test, such as Kruskal-Wallis test, will be used.

**Table 12: Definition of AF cycle length**

Strategy	Initial AF cycle length	Final AF cycle length
PVI	Ablation /Re-ablation CRF C1.3	Ablation / Re-ablation CRF D6
PVI + CFE		Ablation / Re-ablation CRF E7/ D6 ( if E7 is empty)
PVI + Lines		Ablation / Re-ablation CRF F8

### 4. Incidence of repeat procedures

Comparison of the proportion of patients requiring repeat procedures will be made among three treatment groups. If the highest number of repeat procedure is 2, Chi-square test or Fisher exact test will be used. For analysis of 3 or more repeat procedures, the Cochran-Mantel-Haenszel test will be used.

```
proc freq data=crdata.rabl;  
table treatment*n_rabl/chisq cmh;  
run;
```

### 5. Incidence of arrhythmia termination/regularization

Acute termination, defined as in Table 11, will be reported per randomized arm and will be further specified as to whether termination was to another arrhythmia or to sinus rhythm. For both cases, AF termination rates for each ablation strategy will be reported and will be compared between strategies using the chi-square test.



## **6. Improvement in AF burden by > 90% post ablation procedure**

Pre-procedure AF burden is the AF burden at baseline as measured in the three months preceding ablation. For patients that are constantly in AF at baseline, the pre procedure AF burden will be 100%. For the rest of the patients, the pre procedure AF burden will be calculated as below:

$$\frac{\text{the frequency of AF episodes per month} \times \text{the average AF episode duration (hours)}}{30.4 \times 24 \text{ hours}}$$

Post procedure AF burden is the AF burden for the patients at the end of the study. AF occurring within the 3 month blanking period after the first ablation will be excluded. In case that patient does not have an AF recurrence, then the post procedure AF burden is 0%.

Post procedure AF burden will be obtained from the follow up CRF (specifically Table C1.1 and Table F1.1) or via the TTM database. Post procedure AF burden based on CRF can be calculated using formula 1. Post procedure AF burden based on the TTM database will be calculated using formula 2. The maximum of these two values will be used for the analysis.

$$AF \text{ Burden} = \frac{\text{The \# of days in AF between 2 adjacent visits}}{\text{The \# of days between 2 adjacent visits}} \quad (1)$$

$$AF \text{ Burden} = \frac{\text{\# of weeks with at least one TTM of AF}}{\text{\# of weeks of transmission}} \times 100\% \quad (2)$$

The improvement of AF burden will be categorized by a cut off value of 90%, and the number and the percentage of the cases will be reported per randomized arm. Chi-square test will be used for the comparison between the treatment groups, and Fisher exact test will be performed in case 25% of cells have a frequency less than 5.

The same analysis will be performed for AF/AFL/AT burden in addition to AF burden alone.

## **7. Incidence of arrhythmia recurrences of varying durations**

Secondary endpoints #27 - #30 will describe the proportion of patients experiencing recurrences of different durations between study treatment arms at the end of follow-up. Comparison between

the proportions of patients experiencing these durations of recurrences across study arms will be compared by chi-square analysis.

### **8. Incidence of mortality:**

Mortality rate will be reported for each arm. Narrative for the death will be provided in section 2.10.

### **3.2.3 Continuous secondary endpoints**

Each continuous secondary endpoint will be summarized with the number of non-missing value, mean, standard deviation, median and range (interquartile range if necessary) per randomized arm.

#### **1. Mapping time, Procedure duration & Fluoroscopy time**

The procedure duration is specified in the “Ablation” CRF in section H2. The fluoroscopy time is specified in section H3. The mapping time is specified in section H1. The summary statistics will be reported per randomized arm for the first ablation, and the repeated ablations separately.

One way ANOVA will be used for the comparison among the groups, and pairwise comparison will be applied with the p value adjusted using Tukey adjustment. The normality assumption of ANOVA will be tested by the normality test with the aid of QQ plot. In case it is violated, then the equivalent non-parametric test, such as Kruskal-Wallis test, will be used. The equality of variance will be checked by Brown and Forsythe’s test or Levene's test, and with the aid of residual plot. The weighted least square will be used if this assumption is violated. This analysis will be performed for the first ablation and for the second ablations which comply with the randomized strategy. An example of the analysis is shown below:

```
proc anova data=crdata.abl;  
class treatment;  
model proc_min2=treatment;  
means treatment / hovtest=BF welch;  
means treatment/tukey cldiff;  
run;
```

#### **2. Cost utility**

Cost utility will include the following items in case the cost can be retrieved via the reimbursement department.

- GP visit and/or specialist visit related to AF: FU CRF B1;
- Emergency room visit / hospitalization related to AF or procedure: FU CRF B2
- Cardioversion: FU CRF B3

A more detailed version of cost effectiveness analysis is outlined in section 3.2.5.

### **3.2.4 QOL score**

#### **1. SF-36 at baseline, 6, 12 and 18 months after one and/or two ablations**

SF-36 will be summarized according to the 'Manual and Interpretation Guide of SF36', focusing on 8 subscales and the aggregated score. Descriptive statistics will be reported for baseline/ 6/12/18 months. The change of the score at 18 months versus baseline will be reported as well. The same statistical analysis for the procedure time will be applied.

#### **2. EQ-5D at baseline, 6, 12 and 18 months after one and/or two ablations**

The EQ 5D score will be calculated following the guide of EQ-5D. For each dimension, the number and percent will be also reported for each level per randomized arm. These will be reported for baseline/ 6/12/18 months. The change of the EQ-5D score at 18 months versus baseline will be reported and compared using the same statistical method as for the procedure time.

#### **3. CCS SAF at baseline, 6, 12 and 18 months after one and/or two ablations**

The count and percentage will be reported for each level of CCS SAF. Patient will be classified to 'Improved', 'No change' and 'Worsen' at 18 month, compared to baseline score. Mantel-Haenszel test will be used for the analysis.

### **3.2.5 Other pre-specified secondary analyses**

This section describes the analysis which can be performed for the publication. In the CIP, the following secondary analyses were specified as secondary endpoints: Correlation of AF burden to symptoms and quality of life changes; relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome; and evaluation of cost utility. These are all discussed in detail in this section and because they were included in the CIP, they will also be part of the final clinical report. Other analyses listed in this section will not be included in the final clinical report.

#### **1. Comparison between PVI+Lines and PVI**

In case the Kaplan-Meier curve shows a trend that PVI+Lines is differentiated from PVI with regards to the primary endpoint (the time to first recurrence of AF > 30 seconds after one procedure with or without antiarrhythmic medications), post hoc analysis will be performed to assess the treatment effect.

## ***2. Reporting of all primary and secondary endpoints off all antiarrhythmic medications***

The primary endpoint and secondary endpoints in section 1.8 from #1-#13 will also be reported separately without antiarrhythmic medications.

- Antiarrhythmic medications will be defined as class I or class III antiarrhythmics
- Cardiac glycosides, non-sotalol beta-blockers, and calcium channel blockers will not be counted as antiarrhythmics
- Endpoints reported “off antiarrhythmic” medications will be defined as patients who are off antiarrhythmics at the time of the final follow-up

## ***3. Univariable and multivariable predictors of primary or secondary endpoints***

The effect of baseline demographic variables, LA size, ejection fraction, AF history, randomization group, site, ablation of additional arrhythmias, acute AF termination, AF cycle length prolongation, right atrial isthmus ablation, catheter type, and early recurrence of arrhythmia on occurrence of both the primary endpoint and secondary endpoints can be examined. For time to recurrence of an arrhythmia, cox regression analysis will be performed.

## ***4. Effect of ablation strategies in patient subgroups***

The effect of the three ablation strategies will be analyzed in pre-specified patient subgroups typically sub-stratified by the mean or median for continuous data. Variables can be the following (and not limited to) if adequate number of patients permit: age; BMI; gender; hypertension; diabetes; sleep apnea; number of failed antiarrhythmics pre-ablation 0 and 1/2; CHADS score 0/1 and >1; CHADSVASC score 0, 1, 2, and >2; constantly in AF; duration of AF history; ejection fraction; LA size; presence of LA scarring; antiarrhythmics usage at last follow up.

## ***5. Relationship of early or mid-term recurrences on incidence of late recurrences***

The proportion of patients experiencing recurrences of AF and AF/AFL/AT both on and off antiarrhythmic medications will be examined.

The following information will be reported.

- Proportion of patients with AF recurrence after the initial three month blanking period until the end of follow-up (18 months) after one procedure within three months, between 3 and 6 months, between 6 and 12 months, and between 12 and 18 months
- Proportion of patients with AF recurrence after the initial three month blanking period until the end of follow-up (18 months) after two procedures within three months, between 3 and 6 months, between 6 and 12 months, and between 12 and 18 months
- Proportion of patients with AF/AFL/AT recurrence after the initial three month blanking period until the end of follow-up (18 months) after one procedure within three months, between 3 and 6 months, between 6 and 12 months, and between 12 and 18 months
- Proportion of patients with AF/AFL/AT recurrence after the initial three month blanking period until the end of follow-up (18 months) after two procedures within three months, between 3 and 6 months, between 6 and 12 months, and between 12 and 18 months

Patient may have multiple episodes over the study course; therefore, it is interesting to investigate the proportion of patients experiencing recurrences within each time window. The incidence of recurrence will be reported for the overall population. The incidence of recurrences within each time window will be compared between treatment groups using Chi square analysis. The number of episodes occurring in each time period will be compared across groups using a Poisson regression model. Study completion date minus the date of the three month follow-up will be used as the offset.

We will also look at the effect of recurrences in one time period on the incidence of recurrences at different time periods. For example, the occurrence of a recurrence during the first 3 month blanking period could be used to predict late recurrences at 18 months. Or, lack of recurrence at 12 months could be used to predict recurrence (or lack thereof) at 18 months. Repeat ablation will be considered as an AF recurrence for late recurrences. Univariate logistic regression analysis for the proportion of patients experiencing late recurrences or univariate cox regression analysis for the time to recurrence of late recurrences will be used to assess the impact of early on later recurrence. We will also look at the relationship of ablation strategy and early recurrences on later recurrences using the appropriate recurrent event model (e.g. counting event process or stratified Cox approach).

## ***6. Correlation of AF burden to symptoms and quality of life changes***

From section 3.2.2, we will have a calculation of the AF burden for each patient both pre-ablation and post-ablation. Very little is known about the burden of AF, or change in burden of AF, required to affect changes in a patient's quality of life. Although 30 seconds is used to define success in clinical trials of AF ablation, this short duration of AF is unlikely to make a difference in patient quality of life. As part of the secondary endpoints of this study, we collected pre- and post-ablation QOL scores using the EQ5D, SF-36, and CCS SAF scales. Using methods similar to those used in Mantovan et al, Can J Cardiol October 2013, we shall examine the cutoff in both absolute AF burden and change in AF burden required to affect change in quality of life of patients in STAR AF II. Further detailed methodology for this secondary analysis will be provided elsewhere.

### ***7. Relationship of ablating all atrial arrhythmias versus ablation of only targeted endpoints on long term outcome***

We will be collecting the following secondary endpoints (#31 and #32):

- Occurrence of non-AF atrial arrhythmia during the first ablation procedure
- Occurrence of non-AF atrial arrhythmia during the second ablation procedure

If other arrhythmias occurred during the ablation, and if those arrhythmias were targeted, we will compare the outcome of those patients with those in whom there were no additional arrhythmias, and those in whom other arrhythmias occurred but were not ablated. Patients in the first group will be identified if the answer to G1 on the "Ablation" CRF was "Yes" and the answer to G1.1 was "Yes" and the table in G1.1.1 shows an equal number of identified arrhythmias to those successfully ablated. The second group will consist of patients who successfully underwent their randomized strategy but no additional arrhythmias were seen (G1 is "No"). The third group will be patients in whom additional arrhythmias were seen but were not ablated (answer G1 is "Yes" but answer to G1.1 is "No" OR number of arrhythmias present in table G1.1.1 exceeds the number successfully ablated. The log rank test will be used to assess the impact of ablation of additional arrhythmias on long-term procedural outcome, with the aid of Kaplan-Meier curve.

The long term procedural outcome will include primary endpoint as well as the first secondary endpoint 'Freedom from documented AF episodes > 30 seconds at 18 months after two procedures with/without antiarrhythmic medications' as well as the other secondary endpoints of "Freedom from any AF/AFL/AT > 30 seconds at 18 months with/without antiarrhythmic medications" after both one and after two procedures.

### ***8. Evaluation of cost efficacy/benefit***

Cost related information, such as the incidence of cardioversions, emergency room visits, hospitalizations, or urgent care visits during follow-up are collected throughout the study. Overall rates of each will be reported, but they will also be compared according to ablation strategy and according to whether the patient had a successful ablation outcome after both one and two procedures. Chi-square test will be used for the comparison of these health care utilizations. In case more than 25% of the cells count less than 5, the fisher exact test will be used instead.

Cost utility can be the following items in case the cost can be retrieved via the reimbursement department.

- GP visit and/or specialist visit related to AF: FU CRF B1;
- Emergency room visit / hospitalization related to AF or procedure: FU CRF B2
- Cardioversion: FU CRF B3

Other adverse events may be collected from adverse event forms or free comments provided on the CRFs. EQ5D health states can be used to calculate QALYs. Detailed methodology for cost effectiveness analysis will be provided later.

#### 4 Proposed Figures and Tables

The proposed figures and tables listed here are those anticipated for the purposes of publication of the main manuscript. If not included below, all tables and analyses listed in the SAP will or may be requested for table and/or figure generation. Additional tables and/or figures may be requested as the manuscript is being written. Figures and tables required for separate secondary analysis publications will not necessarily be included here.

##### **TABLES:**

- Subject disposition
- Subject disposition by study site
- Summary of demographics and baseline characteristics
- Summary of AF history
- Summary of TTM compliance (overall and between 12 and 18 months)
- Study crossover listings and details
- Study deviation listings and details
- Listing of ITT and As Treated populations overall and by each arm
- Incidence, timing, and number of repeat ablation procedures (for each arm)
- Ablation details (for each arm, for first procedure) including mapping, fluoroscopy and procedure times, AF induction, isoproterenol use, etc.
- Ablation details (for each arm, for repeat procedures) including mapping, fluoroscopy and procedure times, AF induction, isoproterenol use, etc.
- Acute ablation strategy goals achieved (PV isolation, complete CFE ablation, complete linear ablation) – for each arm, first and repeat ablation procedures
- Summary and statistical analysis of achieving strategy goals or not on long-term outcome (secondary endpoints #23-#25)
- Acute ablation results (AF termination, AF regularization, AFCL changes) – for each arm, first and repeat ablation procedures
- Summary and statistical analysis of AF termination/regularization or AFCL changes on long-term outcome (secondary endpoint #22)
- Other ablation performed (occurrence of other atrial arrhythmias, other arrhythmias ablated, right atrial flutter ablation) – for each arm, first and repeat ablation procedures
- Summary and statistical analysis of performing other ablation on long-term outcome by arm and overall
- Summary, proportion, and statistical analysis of primary endpoint including mode of endpoint detection (CRF, Holter, TTM, etc.)



- Summary, proportions, and statistical analyses of secondary endpoints #1-#13 including mode of endpoint detection (CRF, Holter, TTM, etc.)
- Summary, listing and analysis of antiarrhythmic medication use at each follow-up during the study – overall and for each arm
- Summary, listing and analysis of primary endpoint and secondary endpoints #1-#13 off antiarrhythmic medication
- Summary and analysis of AF burden pre- and post-ablation overall and by study arm
- Summary, listing and analysis of adverse events, particularly procedural complications, overall and for each study arm after first procedure
- Summary, listing and analysis of adverse events, particularly procedural complications, overall and for each study arm after repeat procedures
- Summary and statistical analysis of proportion of patients experiencing >1 min, >10 min, > 1 hour, and >24 hours of AF or AF/AFL/AT post-ablation after first and after repeat procedures
- Summary and statistical analysis of number of early, mid, and late recurrences and impact of such recurrences on subsequent recurrence of atrial arrhythmia
- Summary and statistical analysis of health care utilization (such as cardioversion or hospitalization) for patients during the study by arm and overall
- Summary and statistical analysis of univariate multivariate analyses of predictors of primary and secondary endpoints (particularly secondary endpoints #1-#13)
- Summary and statistical analysis of effects of ablation strategies in patient subgroups – male vs female, elderly, large LA size, duration of AF history, etc (see #4 in section 3.2.5)

## FIGURES

- Study disposition flow diagram
- Sample lesion sets for each of the three ablation strategies
- Description and use of CFE mapping algorithm
- Kaplan Meier survival curves for primary endpoint
- Kaplan Meier survival curves for secondary endpoints #1-#13
- Graph of number of repeat procedures overall and in each arm
- Graph of number of patients experiencing recurrence of various durations (>30 sec, >1 min, >10 min, >1 hour, >24 hours) overall and by each arm
- Forest plots of effect of each arm in pre-specified patient subgroups (see #4 in section 3.2.5)

- Kaplan Meier survival curves for outcomes stratified by variables indicated to be significant predictors of outcome by univariable or multivariable analysis (see #3 in section 3.2.5)
- Kaplan Meier survival curves for outcomes stratified by complete PV isolation or not; complete CFE ablation or not; complete linear ablation or not
- Kaplan Meier survival curves for outcomes stratified by AF termination during ablation procedure or not

## 5 Appendix: Abbreviations

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
ANOVA	Analysis of Variance
AT	Atrial Tachycardia
CCS SAF	Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale
CFE	Complex Fractionated Electrograms
CIP	Clinical Investigation Plan
CPL	Clinical Project Leader
CRF	Case Report Form
CT	Computed Tomography
DCF	Data Clarification Form
ECG	Electrocardiogram
EQ-5D	EuroQol Group 5-Dimension
EQ-5D VAS	EuroQol Group 5-Dimension visual Analogue Scale
ID	International Division
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LINES	Empiric Linear Ablation
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PV	Pulmonary Vein
PVI	Pulmonary Vein antrum isolation
QALY	Quality Adjusted Life Year
QOL	Quality Of Life
QQ plot	Quantile-Quantile plots
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SJM	St. Jude Medical
SF-36	Short Form 36

Abbreviation	Term
SVT	Supraventricular Tachycardia
TTM	Trans Telephonic Monitoring

Published methods paper:

Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial-Part II (STAR AF II): design and rationale. Verma A, Sanders P, Macle L. *Am Heart J*. 2012 Jul;164(1):1-6.e6. doi: 10.1016/j.ahj.2012.04.002.