FIRMAP AF Study

Focal Impulse and Rotor Modulation Ablation versus Pulmonary Vein isolation for the Treatment of Paroxysmal Atrial Fibrillation

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1 PROTOCOL SIGNATURE PAGE

Protocol: FIRMAP AF

Confidentiality

I understand that the following is considered confidential: study protocol, study case report forms, study-related documentation including correspondence with the study sponsor, all pre-publication data derived from the study, and technical information that has not been previously made public.

I understand that the contents of this Protocol may not be used in any other clinical study and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation, for example submission to an Ethics Committee; however, I will give prompt notice to the Sponsor of any such disclosure.

Compliance with EC and Protocol Requirements

I have read and agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study or protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to await approval for the protocol and informed consent from the governing EC or equivalent review board, and from the local Ministry of Health (if required) if my site is located outside the United States, before initiating the study. I agree to obtain informed consent from subjects prior to performance of study-specific screening assessments or enrollment in the study. I agree to collect and record data as required by this protocol and case report forms, to prepare annual, final and adverse effect reports as required by this protocol, and to maintain study documentation for the period of time required.

Site Number:	
Printed Name of Investigator:	
Signature of Investigator:	Date of Signature:

2 ABBREVIATIONS and DEFINITIONS

ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial fibrillation
ASD	Atrial septal defect
AT	Atrial tachycardia
CABG	Coronary artery bypass graft (surgery)
CAD	Coronary artery disease
CBC	Complete blood count
CFAE	Complex fractionated atrial electrograms
$CHADS_2$	Scoring system in determining stroke risk for those with AF
CHA_2DS_2-VASc	Scoring system in determining stroke risk for those with AF (Congestive heartfailure, Hypertension, Age >75 years, Diabetes, Stroke/TIA, Vascular Disease, Age, Sex category
CIED	Cardiac implanted electronic device
CL	Cycle length
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed tomography
CTI	Cavotriscuspid isthmus
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HCG	Human chorionic gonadotrophin
HIPAA	Health Insurance Portability and Accountability Act
HRQL	Health Related Quality of Life, a subscale of the UFS-QOL
ICE	Intracardiac echocardiography
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
LAA	Left atrial appendage
LMWH	Low-molecular-weight heparin
LV	Left ventricle
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
PVI	Pulmonary vein isolation
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
TIA	Transient ischemic attack
UADE	Unanticipated Adverse Device Effect

3 BACKGROUND AND RATIONALE

Atrial fibrillation (AF) is the most common sustained arrhythmia in man, and has an increasing population prevalence over time. Treatment is aimed at stroke prevention on the one hand, and amelioration of symptoms (palpitations, lightheadedness, dyspnea, fatigue) due to the arrhythmia. Medical therapy often fails to render a satisfactory response for the latter, prompting the search for alternative therapies. Surgical and, in the last 15 years, catheter ablation techniques have been devised to try to prevent episodes from starting. Groundbreaking work by Haïssaguerre[1] showed that premature discharges or rapid repeated firing from the pulmonary veins (PVs) could trigger AF episodes and that electrical isolation of the PVs could potentially cure the patient of AF. PV isolation currently is a painstaking process consisting of delivering radiofrequency energy or cryoablation in the left atrium to isolate these veins. Such procedures take 2-5 hr. to be completed depending on the complexity of the individual case, and a majority of patients require a 2nd or even 3rd procedure to achieve acceptable antiarrhythmic results. Despite considerable investigative effort, the exact pathophysiology of how PV triggers initiate and or maintain episodes of AF has been elusive.

Recently, a novel mapping technology (RhythmView, Abbott, Menlo Park, CA) based upon the work by Narayan et al[2] has been developed for analyzing atrial recordings during human AF, finding that >95% of cases demonstrate either a rapidly spinning rotor (small circuit) or very rapid focal impulse formation. Furthermore, they have shown that catheter ablation at these relatively circumscribed areas can significantly affect AF, either by substantial slowing of the rate or termination (to an atrial tachycardia or sinus rhythm). In the CONFIRM (CONventional vs Focal Impulse and Rotor Modulation) trial, patients were treated with either conventional mapping and ablation (largely PV isolation or PVI) vs ablation of rotors or sites of focal impulse formation as designated by the mapping algorithm, followed by conventional ablation (PVI). The authors found much higher acute and long-term efficacy when focal impulse and rotor modulation (FIRM procedure) was used (82.4 vs 44% freedom from AF at 24 months post procedure). Although CONFIRM was a controlled study, a randomized evaluation would be warranted.

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[1] Haïssaguerre M, Jaïs P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339: 659–66.

[2] Narayan,S.M., D.E. Krummen, P. Clopton, K. Shivkumar and J.M. Miller. Direct Or Coincidental Elimination of Stable Rotors or Focal Sources May Explain Successful Atrial Fibrillation Ablation: On-Treatment Analysis of the CONFIRM (CONventional ablation for AF with or without Focal Impulse and Rotor Modulation) Trial. Journal of the American College of Cardiology (2013) 62:138-147.

FIRMAP-AF is a prospective, multicenter, randomized, controlled study to assess the safety and effectiveness of FIRM-guided ablation procedures versus a standard conventional procedure with PVI for the treatment of symptomatic paroxysmal atrial fibrillation.

3.1 RATIONALE

According to the American Heart Association, atrial fibrillation affects approximately 2 million Americans. Atrial fibrillation may reduce cardiac performance and may result in thrombus formation in the left atrium and thromboembolic events, such as stroke. Approximately 15% of all strokes occur in people with atrial fibrillation. Ablation of atrial fibrillation that specifically targets approximately 2-5 mm outside of the pulmonary vein is currently a standard of care treatment in subjects with symptomatic atrial fibrillation who have failed drug therapy. Unfortunately, this procedure is time consuming, creates substantial damage in the left atrium due to the number of lesions required, and has mixed success with the best outcomes being 50-80% freedom from symptoms at 1 year post ablation. Also, as with any invasive procedure, patient complications may heighten with increased time and additional radiation exposure.

One of the major issues with the current procedure is the lack of knowledge about the critical regions of the heart that have the source rhythms causing and sustaining AF. Some very new technology developed based upon work done under NIH support at the University of California San Diego has shown promise in diagnosing these key source rhythms. Ablation to target these sources, called Focal Impulse and Rotor Modulation (FIRM) guided procedure, shows promise but need to be evaluated further.

3.2 HYPOTHESIS

Focal Impulse and Rotor Modulation (FIRM) guided procedures will eliminate the source of clinical arrhythmias in subjects with indications for AF ablation procedures.

4 STUDY OBJECTIVES

The primary objective is to compare the safety and effectiveness of FIRM-guided ablation procedures with conventional RF based pulmonary vein isolation ablation procedure for the treatment of paroxysmal atrial fibrillation (AF) for subjects without prior AF catheter ablation.

The secondary objective is to evaluate the treatment time and quality of life outcomes.

5 STUDY DESIGN

The study is designed as a prospective, multicenter, single-blind, randomized study to assess the safety and effectiveness of FIRM-guided RF ablation procedures for the treatment of symptomatic paroxysmal atrial fibrillation. The subjects will be blinded to study treatment for the duration of the study period.

5.1 SAMPLE SIZE

A total of 170 subjects at up to 15 investigative sites will be enrolled and equally (1:1) randomized between those undergoing conventional RF ablation with confirmation of PVI vs. those treated with FIRM-guided conventional RF ablation without PVI. Additionally, ablation of any atrial tachycardias (AT) and/or the cavotricuspid isthmus may be performed in those subjects with documented AT/atrial flutter.

5.2 RANDOMIZATION

Block randomization stratified by center will be used to assign subjects (1:1) to the conventional RF ablation treatment with PVI (PVI group), or to the FIRM-guided AF ablation procedure without PVI (FIRM group).

5.3 STUDY DURATION

Overall study duration (first subject enrolled through last subject exit) will be comprised of approximately 18 months of enrollment period. Study duration for an individual subject, once consented, will be up to 1 month for screening (including baseline measurements) and 12 months for follow-up after treatment for a total duration of approximately 13 months.

6 ENDPOINTS

6.1 PRIMARY EFFECTIVENESS ENDPOINT

Effectiveness endpoint is defined in the table below.

Table 1 – Primary Effectiveness Endpoint

Endpoint	Definition
Long term success	Single-procedure freedom from AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period). * Freedom from AF/AT recurrence is defined as no documented episodes of AF/AT > 30 seconds with conventional non-invasive monitoring. In the case of a cardiac implanted electronic device (CIED), freedom from AF recurrence is defined as no documented episodes of AF/AT > 30 seconds in a 72-hour window at the follow-up visits in addition to any symptomatic episodes with documented AF > 30 seconds. AT recurrence does not include episodes of CTI (cavotricuspid isthmus) dependent flutter.

6.2 SECONDARY ENDPOINTS

Secondary endpoints are defined in Table 3 below. This study will also collect data relating to the health economics of the FIRM-guided procedure to conduct additional evaluations if primary endpoints are met.

Table 2 – Secondary Endpoints

Endpoint	Definition
Acute Effectiveness	1. FIRM group: Elimination of identified AF rotors 2. Control group: Isolation of all pulmonary veins

Additional Secondary (unpowered) Effectiveness	1) AF termination or CL prolongation, as identified by: a. Termination of spontaneous or induced AF by ablation of the source of arrhythmia. b. Reduction of the mean AF rate by at least 10% by ablation of the source of arrhythmia. 2) Single-procedure freedom from AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period) (Long-Term Effectiveness). 3) Freedom from symptomatic AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period) (Long-Term Effectiveness). 4) Freedom from AF recurrence from 0-12 months post index ablation procedure (without 90-day blanking period) (Long-Term Effectiveness). 5) Freedom from AF recurrence at 12 months post index ablation procedure (can include repeat procedures).
Acute Safety Endpoint	1. Freedom from procedure-related serious adverse events within 7 days of the procedure.
Long-Term Safe Endpoint	1. Freedom from procedure-related serious adverse events within one year of the index procedure.

Table 3 – Additional Evaluations

Parameter	Definition

Total RF ablation time	Total RF ablation time as measured by total time of ablation lesion applications will be documented. These values will be compared between the FIRM-guided and conventional ablation groups. If ablation for AT/atrial flutter is pursued, this ablation time will be documented separately
Total radiation exposure	As above, these values will be compared between the FIRM-guided and PVI groups.
Repeat procedure and hospitalization	Any information regarding repeat procedures and re-hospitalizations will be collected and compared between groups
Quality of Life	Impact on quality of life, using patient-reported outcome instruments (EQ-5D and AFEQT), within treatment groups (change from pre-procedure to post-procedure follow-up timepoints) and between treatment groups. Analysis will be performed if primary endpoints are met.
Economic Analysis	Cost-effectiveness analysis based on clinical and patient-reported outcomes and resource utilization. Analysis will be performed if primary endpoints are met.

7 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

7.1 SELECTION CRITERIA

The criteria listed below shall be used to determine if a participant is eligible for entry into the study. A subject must meet ALL of the study inclusion criteria and NONE of the study exclusion criteria in order to be considered eligible for participation.

A. *Inclusion Criteria*

Subjects are required to meet the following inclusion criteria:

1. Male or female 18 – 80 years of age.
2. Experiencing at least two (2) documented episodes of **paroxysmal** atrial fibrillation in the last 3 months preceding study entry with clinical indication for AF ablation per guidelines. At least one episode should be documented by rhythm strip or ECG.
3. Indicated for AF ablation according to current EHRA guidelines.
4. Prescribed with oral anticoagulation therapy, in indicated patients per the latest EHRA guidelines.
5. Willingness and able to remain on anti-coagulation therapy as per the latest EHRA guidelines.
6. Left atrial diameter < 5.5 cm as measured and image ((CT/TEE/TTE/ MRI or ICE) documented within previous six months up to pre-procedure.
7. Sustained AF (>5 min uninterrupted) during the electrophysiology procedure. If the subject is not experiencing spontaneous, sustained AF, it may be induced by burst pacing (typically from the coronary sinus) with or without isoproterenol infusion in conventional clinical fashion.
8. Willingness, ability and commitment to participate in baseline and follow-up evaluations.
9. Signed patient informed consent form.

B. *Exclusion Criteria*

Subjects must NOT meet any of the following exclusion criteria:

1. Presence of structural heart disease of clinical significance including:
   a. Coronary artery disease with either:
      i. Coronary artery bypass surgery (CABG) within the last 180 days (six months), or
      ii. Stable/unstable angina or ongoing myocardial ischemia.

b. Congenital heart disease where either the underlying abnormality or its correction prohibits or increases the risk of ablation.

2. NYHA Class III – IV.
3. Ejection fraction < 40% (within previous six months).
4. History of myocardial infarction (MI) within the past three months.
5. Any concomitant arrhythmia or therapy that could interfere with the interpretation of the results from this study.
6. ASD closure device, LAA closure device, prosthetic mitral or tricuspid valve, or permanent pacemaker.
7. Any previous AF catheter ablation.
8. History of prior cardioversion for AF lasting > 48 hours.
9. Continuous AF episode lasting > 7 days immediately prior to the procedure without a sinus rhythm.
10. Severe electrolyte abnormalities at time of the ablation procedure or atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible non-cardiac cause.
11. Atrial fibrillation from a reversible cause (e.g., surgery, hyperthyroidism, pericarditis).
12. Contraindication to Heparin and Warfarin/other novel oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban).
13. History of pulmonary embolus within one year of enrollment.
14. Acute pulmonary edema.
15. Atrial clot/thrombus on imaging such as on a trans-esophageal echocardiogram (TEE) performed within 72 hours of the procedure if deemed appropriate by investigator.
16. History of a cerebrovascular disease (including stroke or TIA) within the last 12 months.
17. Any anticipation of cardiac transplantation or other cardiac surgery within the next 12 months.
18. History of thromboembolic event within the past 3 months.
19. Diagnosed atrial myxoma.
20. Significant pulmonary disease, (e.g. restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms and significantly increases risk to sedation or anesthesia.

21. Acute illness or active systemic infection or sepsis.
22. Known genetic bleeding disorders such as blood clotting abnormalities or bleeding abnormalities, not related to arrhythmia or the management of arrhythmia.
23. Life expectancy of less than 12 months.
24. Presence of intramural thrombus, tumor, or other abnormality that precludes catheter introduction or safe manipulation.
25. Women who are pregnant.

7.2 INFORMED CONSENT

The investigator will obtain written informed consent from the subject using the EC-approved consent form prior to initiation of any study-specific assessments or procedures. Consent is documented by the dated signatures of the subject the person conducting the consent discussion, and the investigator. Written informed consent must be obtained from a potential subject no more than 90 days prior to performing the study procedure.

Informed consent completion will be monitored regularly by the sponsor.

7.3 MOMENT OF ENROLLMENT

The subject will be considered "enrolled" in the study after the subject has met all inclusion and exclusion criteria, has signed the study informed consent form, and has completed the baseline assessments.

7.4 RANDOMIZATION AND SUBJECT IDENTIFICATION

Randomization will occur if the subject is deemed eligible following screening baseline assessments and has signed the study informed consent form. Subject identification number will be assigned at the time of randomization and the identification number will be retained throughout the study. No personal identifying information will be included on the case report forms.

7.5 SUBJECT DISCONTINUATION OR WITHDRAWAL

The investigator should instruct the subject regarding the importance of complying with the data collection and follow-up visit requirements. Poor subject adherence may result in the sponsor discontinuing the subject from the study.

Subjects may be involuntarily removed from the study for failure to adhere to the protocol, failure to attend follow-up visits, or due to safety reasons. In

such cases, the investigator shall arrange for an exit visit and complete a study exit case report form for the subject.

Subjects may voluntarily withdraw from the study at any time without reason. The investigator shall make an effort to obtain an exit visit but cannot insist on the visit if the subject does not wish to come in. The investigator shall complete a study exit case report form with as much information as is available at the time of withdrawal.

A subject may be withdrawn after screening and before receiving the study treatment if, at the investigator's discretion, he or she has developed a general health condition that would increase risks from study treatment.

7.6 CONTACT FOR FOLLOW-UP AND LOSS TO FOLLOW-UP

Subjects who miss a study visit should be contacted immediately by the Investigational Site to determine the reason for the missed visit and to reschedule the visit as soon as possible to meet the study visit window. If the subject cannot be located after 3 attempts through a variety of communication modes (phone, email, letter), then the subject will be considered lost to follow-up. The investigational sites should collect contact information (home phone, cell phone, fax, email, home address, etc.) from the subject in order to minimize loss to follow-up. All attempts to contact the subjects will be documented and retained in the subject study record.

8 INVESTIGATIVE SITES

Up to 20 investigational sites in Europe will participate in this study.

8.1 INVESTIGATOR SELECTION

A. To qualify for participation, the study investigator will have completed the following:

- Undergone the standard training provided by Abbott EP (Topera, Inc.) in the use of the RhythmView® system and analysis of FIRMap® produced by the system
- Participated in 10 FIRM-guided procedures prior to enrolling any subjects in the study.

8.2 EQUIPMENT REQUIREMENT

A. In order to participate in this study, the site must also have the following equipment available:

- 64-pole mapping catheter (FIRMap Catheter) and appropriate analyzer to acquire full chamber data (RA or LA) per Abbott EP RhythmView system requirements.
- Abbott EP RhythmView 3D electrophysiologic mapping system.
- Optionally, 3-D electroanatomic mapping system (CARTO, Biosense Webster, Velocity or Nav-X, St Jude Medical) compatible with FIRMap for documentation of lesions relative to recordings from mapping catheter.

8.3 INVESTIGATOR DISCONTINUATION

Prior to participation in the study, all investigators must sign the Protocol Signature Page, which outlines the investigator's obligations in the study. The sponsor may elect to discontinue, or suspend, the investigator's participation in the study due to poor study compliance, lack of compliance with applicable regulations or EC requirements, or insufficient recruitment of study subjects.

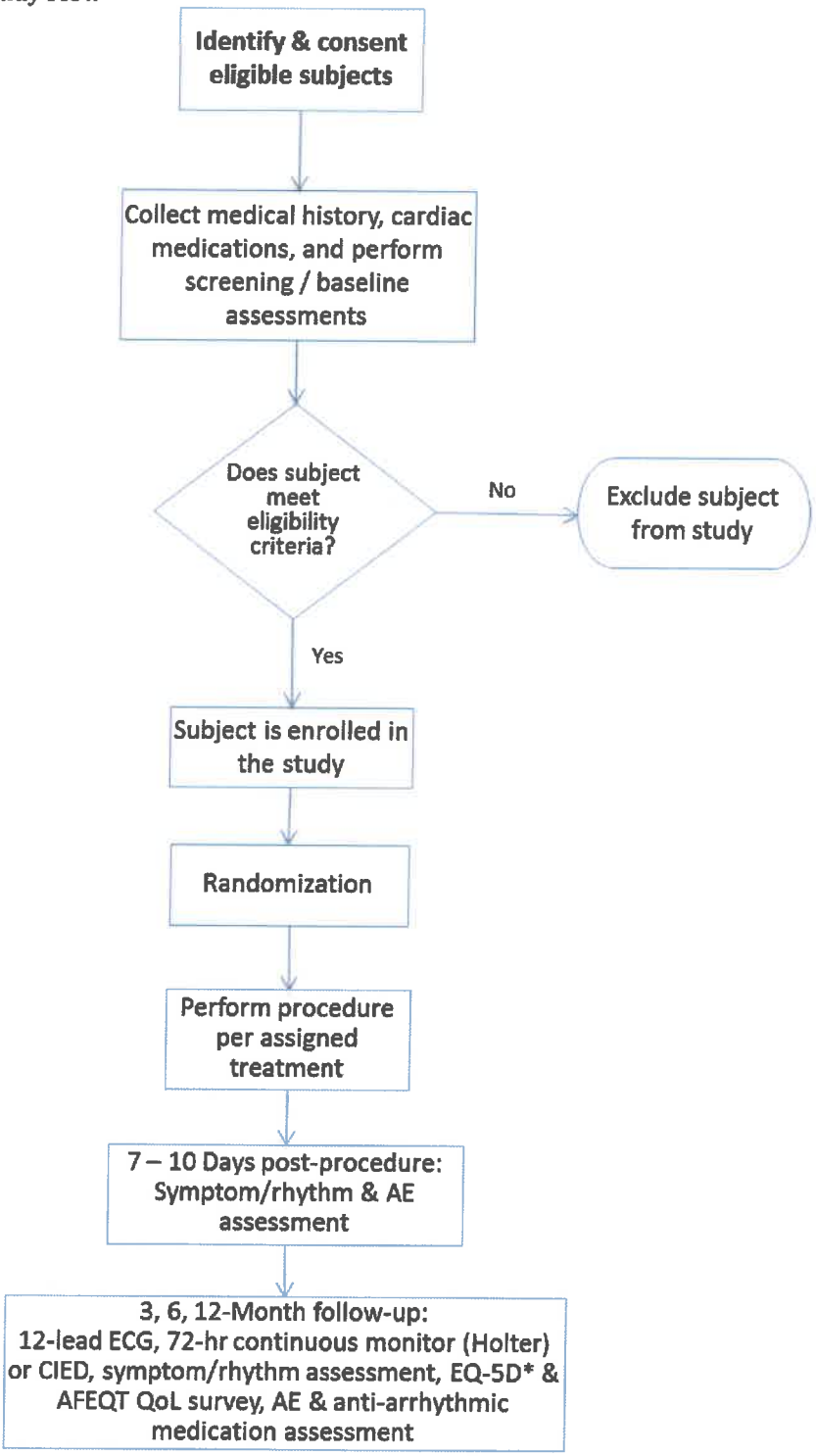
9 STUDY FLOW AND VISIT SCHEDULE

The study will be conducted in three phases listed below and depicted in Figure 1.

1. Screening & Baseline
2. Study procedure through discharge
3. Follow-up periods

Each of these phases is discussed separately below, following Table 5 – Schedule of Assessments.

Figure 1 Study Flow



*EQ-5D QoL survey will be collected monthly post-procedure. Scheduling may be changed based on patient compliance.

Table 4 – Schedule of Assessments

Event	Baseline	Procedure	Discharge	3-month	6-month	12-month
Informed consent	✪					
Demographics, medical history, cardiac diagnosis	✪					
Lab work, collected per institution's standard of care	✪					
INR if patient is on Warfarin (as appropriate on post-procedure f/u)	✪			✪	✪	✪
TEE (when clinically indicated)	✪					
Diagnostic 12-lead ECG	✪		✪	✪	✪	✪
Documentation of symptomatic PAF	✪					
Concomitant cardiac medications	✪		✪	✪	✪	✪
NYHA Class Assessment	✪					
EHRA Class Assessment	✪					✪
[1] EQ-5D QoL Survey	✪			✪	✪	✪
AFEQT QoL Survey	✪			✪	✪	✪
AF symptom and rhythm assessment	✪		✪	✪	✪	✪
Ablation procedure		✪				
AF interventional procedure(s) performed (repeat ablation, AF-related hospitalization)			▩	▩	▩	▩
AE assessment		✪	✪	✪	✪	✪
72-hour ambulatory continuous ECG monitor (Holter) OR interrogation of CIED, as applicable	▩			✪	✪	✪

[1] The ED-5D QoL survey will be completed on a monthly basis post index procedure. Scheduling may be changed based on patient compliance.

Legend: ✪ = Required ▩ = if applicable

9.1 SCREENING AND BASELINE

A. *Screening*

Patients at the investigational sites with symptomatic paroxysmal AF will be asked about their interest in study participation. For those patients who express an interest to participate, the inclusion/exclusion criteria will be reviewed against existing medical history and the results of any standard clinical work-up to assess preliminary eligibility. Potential patients who do not meet entrance criteria may, as appropriate, repeat screening evaluations at a later time for possible enrollment into the study.

B. *Baseline Assessment*

If the patient is not excluded on the basis of existing medical history and standard clinical work-up, the patient will be asked to provide informed consent to participate in the study. Baseline assessments include the following as shown in Table 5 – Schedule of Assessments.

- Determine study eligibility based on the requirements specified in the inclusion / exclusion criteria.
- Demographics.
- Medical history, including any hospitalizations or emergency room visits for episodes of all cardiac arrhythmias within six months of screening, all anti-arrhythmic drugs (AADs) and other cardiac medications.
- Reported incidence of at least two (2) documented episodes of symptomatic paroxysmal AF during the three months preceding trial entry (at least one episode should be documented by rhythm strip, CIED or ECG).
- Treatments administered for atrial fibrillation in the six months prior to enrollment, e.g., pharmacologic treatments and non-pharmacologic interventions. Medications should include dose and duration.
- Documentation of therapeutic International Normalization Ratio (INR) for three weeks prior to the procedure (if applicable per Inclusion Criteria) in cases of subjects taking warfarin.
- NYHA class.
- EHRA class.
- Current cardiac rhythm.
- Largest dimension left atrial diameter measured within the last 3 months or from transthoracic echo, cardiac CT or cardiac MR with image documentation. Intracardiac echocardiographic measurement at the time of the procedure can alternatively be used to document this.

- Ejection fraction (EF) measured within the last 3 months or from the pre-procedure TEE or TTE.
- When clinically indicated, TEE will be performed within 72 hours prior to the ablation procedure. If any evidence of left atrial thrombus is discovered, then the ablation procedure will not be performed at that time. The patient may be either excluded from the study or maintained on oral anticoagulation for an additional period of at least 6 weeks and re-tested (TEE repeated) for thrombi.
- If the patient has a preexisting CIED, interrogation of the device will be performed to document AF burden in the 1-2 months preceding the procedure.
- 12-Lead ECG within 72 hours of, or immediately prior to, study procedure.
- Cardiac medications currently prescribed for the subject's daily medical therapy.
- Laboratory values TSH, Electrolytes (sodium, potassium) and Creatinine
- Neurological Exam (if clinically indicated) if symptoms suggestive of neurologic disease, and is to be performed by the neurology medical staff.
- Prior to the procedure, anticoagulation therapy will be performed as per institutional standard.
- EQ-5D and AFEQT Quality of Life survey.

9.2 STUDY PROCEDURE

A. *Pre-procedure Preparation*

Just prior to and/or during the procedure, a glycoprotein IIb/IIIa inhibitor or other platelet inhibitor may be administered if it is standard practice. If the FIRMap catheter is to be used, heparin should be administered prior to insertion per local protocol in order to achieve and maintain ACT > 300. Heparin should be administered immediately following transeptal puncture in the case that ACT is not >300.

B. *Intra-procedure Guidelines*

During the procedure, the following actions should be taken and appropriate data collected. Table 6.

Table 5 – Intra-Procedure Guidelines

Parameter	Description

Vascular access	Under sterile technique, the right and/or left femoral veins may be cannulated via Seldinger, or percutaneous approach. Other vascular access also may be obtained based upon physician judgment.
Reference catheter placement	Reference catheters (including 64-pole FIRMap catheter(s)) s may be inserted and placed within the heart to record signals as clinically required at the discretion of the physician.
Access to left atrium	Access to the left atrium should be made according to the institution's standard practice.
Anticoagulation	Heparin should be administered per local protocol in order to achieve and maintain ACT > 300 prior to insertion of FIRMap catheter, if applicable. Heparin should be administered immediately following transeptal puncture in the case that ACT is not >300.
Catheter placement	Catheters may be inserted and used according to the institution's standard practice.
Source arrhythmia diagnosis	**For FIRMap patients only:** After obtaining at least 1 minute of continuous electrograms from the 64-pole FIRMap catheter either simultaneously or sequentially in the right and left atria, these electrogram data will be transferred to the RhythmView system. Right atrial mapping will initially be performed. If no right atrial rotor/source is detected or all right atrial rotors are eliminated, left atrial mapping will be performed. This will then produce FIRMap displays which will be interpreted by the operator to determine which locations have focal or rotor rhythms that could be sources of the AF.
3-D Electroanatomic Mapping	3-D electroanatomic maps may be created using CARTO (Biosense Webster, Johnson & Johnson) or Nav-X (St. Jude Medical) systems for documentation of anatomy and ablation lesion locations.
Induction of sustained AF	If the patient is not experiencing spontaneous, sustained AF (>5 min uninterrupted), induce sustained AF by atrial burst pacing from a catheter positioned within the CS or left atrial appendage until the atrial refractory period is reached or AF is induced with or without isoproterenol infusion. IF AF CANNOT BE SUSTAINED, THE PATIENT DOES NOT MEET THE INCLUSION CRITERIA FOR THE PROTOCOL AND THE PATIENT WILL UNDERGO CONVENTIONAL AF ABLATION PER PHYSICIAN DISCRETION.
Ablation data	For each ablation, the following data will be recorded: time, catheter size, lesion number, duration of application, average and maximum temperature.

FIRM-guided procedure	Under fluoroscopic guidance, a cardiac ablation catheter is passed to the location(s) identified as AF source rhythms (rotors or focal impulses). FIRM-guided ablation is performed at sites identified by the initial or repeated FIRMap. Such ablation typically consists of 3-5 minutes of ablation in the rotor core region followed by repeat mapping to confirm that the rotor has been eliminated. Following each FIRM guided site ablation, FIRM map is repeated and is followed by rotor ablation until all rotors are eliminated or AF terminates and remains noninducible. If AF terminates and is noninducible prior to repeat mapping, ablation of any identified and targeted rotor core region should be completed fully (e.g. ablation of the anatomic region with 3D electroanatomic guidance). In this FIRM-guided ablation arm, no PV isolation is performed. In case a rotor is located inside the PVs, focal ablation of the rotor (but no PVI) can be performed if the risk for PV stenosis is considered to be minimal as per discretion of the operator.
Conventional Ablation	Conventional ablation consists of isolation of all four pulmonary veins with confirmed entrance block assessed by a multipolar catheter.
Additional ablation for other arrhythmias (non-AF)	Additional ablation for other arrhythmias will be noted for atrial tachycardia (AT) and/or right cavo-tricuspid isthmus ablation in the event that the patient has documented AT/atrial flutter prior to or during the procedure.
ACT values	Activated Clotting Times (ACT) value is first measured prior to insertion of FIRMap catheter or trans-septal puncture, whichever comes first, to determine baseline value and then every 30 minutes post-heparinization until therapeutic and, subsequently, every 30 minutes during left-atrial access. (Heparin dosage should be adjusted to maintain ACT above 300 sec). The ACT will be monitored every 30 minutes following initial heparin delivery until the target value is achieved and subsequently checked at least every thirty minutes during the procedure.
Vascular access sheath removal	The vascular access sheaths will be removed according to the institutional standard.

The following precautions should be taken per standard of practice:

- Typically, in order to reduce the risk of introducing air emboli through a transseptal sheath into the left atrium, the following precautions are taken:

- Aspiration or spontaneous bleed back from the trans-septal sheath side-port may be performed after each catheter withdrawal
- Trans-septal catheter insertion and withdrawal will always be performed slowly
- Unnecessary catheter exchanges may be avoided
- The time any trans-septal sheath is through the septum may be minimized
- The time multiple sheaths cross the septum may be minimized.

- Just prior to ablation, at each ablation site close to the right superior PV or in the posterior RA, pacing at high output (>15 mA) from the ablation catheter tip or fluoroscopic visualization of diaphragmatic movement may be used to assess whether the phrenic nerve is in proximity to the ablation zone. These data will be documented and used to guide ablation at each site.
- Esophageal temperature monitoring during ablation in the posterior LA, per local standard of care, may also be considered.

C. ***Intra-procedure Measurements***

The following data will be collected during the procedure. Table 6.

Data	Description
Fluoroscopy times	To be recorded: *Total fluoroscopy time* • The total fluoroscopy time for the procedure (a.k.a., "pedal down" time)
Total RF ablation time	Total RF ablation time as measured by total time of ablation lesion applications, from first ablation lesion to end of last lesion, will be documented. These values will be noted in both the FIRM-guided and conventional ablation groups. If ablation for AT/atrial flutter is pursued, this ablation time will be documented separately
Total procedure time	Total procedure time defined as: time from insertion of first sheaths for vascular access to removal of sheaths.
Medication administration	Cardiac medications administered during the procedure including drug name, dosage, and indication and will be recorded.
Devices and equipment	Devices and equipment used during the procedure including access devices, diagnostic and ablation catheters, and mapping equipment type will be recorded.

D. ***Post-procedure & Discharge Requirements***

The measurements and evaluations that will occur at post-procedure are provided below.

- Post-ablation and following recovery from anesthesia, subjects will be monitored until stable.

- Post-procedure OAC will be performed according to the institutional standard and the most recent international guideline recommendations.

- Post-procedure drug therapy will include re-initiation and/or continuation of any pre-procedure cardiac medications. Administration of anti-arrhythmic drugs is allowed in the first three months post procedure only. Supplemental anti-arrhythmic medications will be administered under the direction of the investigator and documented in the appropriate section(s) of the case report forms.

- Post procedure rhythm monitoring will occur via a 72-hour ambulatory continuous ECG monitor (Holter) or a Cardiac Implanted Electronic Device (CIED). CIED recordings will be censured for only noting events during the 72 hours preceding the 3, 6, and 12-month follow-up evaluations.

- Pre-discharge evaluation will include:
  - Diagnostic 12-lead ECG
  - Symptom and rhythm assessment
  - Antiarrhythmic medications
  - Adverse event documentation and treatment, as necessary.

9.3 FOLLOW-UP REQUIREMENTS

- ***Follow-Up Visit Schedule***

Each enrolled subject will return for visits with the electrophysiologist in accordance with Table 8 below. The day of the study procedure represents Day 0. Study visits that do not occur within the below time windows will be considered protocol deviations.

Table 7 Follow-up (FU) Visit Windows

Visit	Allowed Visit Date Range
Day 7 to 10 days (Phone or visit)	N/A
3 months (90 days)	± 2 weeks
6 months (180 days)	± 2 weeks
12 months (360 days)	± 4 weeks

- ***Resolution Period***

Following ablation treatment, subjects will undergo a 90-day "resolution" period (aka "blanking period") where medical therapy may be optimized and where any of the procedurally-derived arrhythmias that commonly follow ablation procedures may resolve. During this period, adverse events will be accumulated but primary efficacy measurements will not be performed. In case of repeat ablation is solely for treatment of common type (cavo-tricuspid isthmus dependent) flutter, the patient has not failed the primary long-term efficacy endpoint.

Note: During the 90-day resolution period, medications may be adjusted as medically indicated, and as indicated in above section. Any clinically indicated changes must be documented along with the reason for change.

- ***Anti-arrhythmic Medications***

Anti-arrhythmic medications can be discontinued anytime from Day 91 to Day 180 post-procedure. The date of discontinuation will be determined by each investigator on a patient-by-patient basis, but must occur sometime from Day 91 to Day 180 post-procedure.

- ***Recurrence of AF***

If re-ablation for AF (not including common type atrial flutter) is necessary after documentation of the recurrent arrhythmia has

occurred, the patient will be considered a primary efficacy study failure but still followed up for AF burden.

A. ***Day 7-10 Follow-Up***

(Phone Call or visit at investigator's discretion)

- Subjects will be asked if they have experienced any untoward medical occurrences since the study procedure. If so, these events will be recorded on the Adverse Event form.
- Symptom and rhythm assessment.

B. ***Three-Month Follow-up (± 2 weeks)***

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation 72 hours prior to visit, as applicable
- EQ-5D and AFEQT Quality of Life survey
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation

C. ***Six-Month Follow-up (±2 weeks)***

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation 72 hours prior to visit, as applicable
- EQ-5D and AFEQT Quality of Life survey
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation

D. ***Twelve-Month Follow-up (±4 weeks)***

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation 72 hours prior to visit, as applicable
- EQ-5D and AFEQT Quality of Life survey
- Symptom and rhythm assessment
- EHRA class assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation

E. ***Additional Follow-up***

Subjects will be asked to complete the EQ-5D survey monthly, starting at 1 month post-procedure through the 12-month follow up period. The frequency of survey completion may be changed if inadequate patient compliance is observed.

F. ***Unscheduled Follow-up Visit***

The following assessments/procedures may include:

- Diagnostic 12-lead ECG
- 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation 72 hours prior to visit, as applicable
- EQ-5D and AFEQT Quality of Life survey
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation

10 ADVERSE EVENTS

At enrollment, time of procedure, and at each post-procedure visit the subject will be evaluated for any complications or adverse event. The Investigator will be required to provide the Sponsor with any information concerning any findings that suggest any adverse events/complications pertinent to the investigation. All AEs occurring during the study will be recorded on the appropriate e-CRFs.

Subjects will be carefully monitored during the study for possible AEs. Any AE observed will be fully investigated by the Investigator and classified in line with the definitions below. All adverse events will be followed until resolution or until the Investigator judges the outcome to be chronic or stable.

10.1 DEFINITIONS

Adverse events will be reported and classified by the Investigator using the specific signs, symptoms or abnormal laboratory values, or medical diagnosis if no signs, symptoms or abnormal laboratory values can be identified. The Investigator will classify the adverse events based on the definitions as follows (EN ISO/FDIS 14155:2010):

- **Adverse Event (AE)** - Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons

whether or not related to the investigational medical device.

NOTE 1: This includes events related to the procedures involved.
NOTE 2: For users or other persons this is restricted to events related to the investigational medical device.

- **Serious Adverse Event (SAE)** - Adverse Event that
  - Led to death
  - Led to a serious deterioration in the health of the subject that either:
  - resulted in a life-threatening illness or injury*, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function**.
  - Led to fetal distress, fetal death or congenital abnormality or birth defect

NOTE 1:
* In this context, the term refers to an event in which the subject was at immediate risk of death at the time of the event; it does NOT refer to an event that might have caused death if it were more severe.
** For example, if the occurrence of a "catheter insertion site hematoma" or an "AV fistula" requires a blood transfusion and/or surgical repair, it should be considered a serious adverse event.

NOTE 2:
- Preplanned hospitalizations for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.
- Emergency room visits that do not result in hospitalization (i.e., an overnight stay) should be evaluated for one of the other serious outcomes to determine if they qualify as SAEs.

- **Unanticipated Adverse Device Effect (UADE)** - Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.2 ADVERSE EVENT EVALUATION AND REPORTING

- ***Relatedness***

The investigator will assess each adverse event for its relationship to the study device, and whether it was anticipated in the protocol. The determination of the level of relatedness of the adverse event to the study device or procedure will be made according to the definitions below

  - Device Related: The adverse event was directly and clearly related to the device or procedure
  - Not Device Related
  - Unknown

Adverse events that are serious and/or unanticipated will be reviewed immediately by the AEP Medical Monitor and will also be reviewed by the Clinical Event Committee (CEC).

- ***AE Reporting***

Conditions or diseases which are pre-existing and chronic should not be recorded as adverse events (e.g. AF recurrence). Changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered adverse events. Pre-existing conditions or diseases should be documented as part of the subject's medical history.

Elective or pre-planned treatments for atrial fibrillation (e.g. scheduled re-ablation or cardioversion) which are part of the subject's scheduled treatment plan should not be considered adverse events. However, any events related to a procedure (including re-do procedures) or the patient's underlying atrial fibrillation which were not expected or indicate a worsening of condition should be reported as adverse events. (example: procedure-related perforation or cardiac tamponade).

Every effort should be made to report the underlying condition or final diagnosis for the event. The adverse event should be recorded in standard medical terminology rather than the subject's own words when possible. Signs and symptoms that are considered unrelated to an encountered condition or disease should be recorded as individual adverse events (e.g. if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual adverse event). In contrast, adverse events that occur secondary to other events (e.g. sequelae), if clearly identifiable, should

be identified by the primary cause (example: bradycardia → dizziness → fainting; the primary adverse event is bradycardia).

- ***SAE Reporting***

All serious adverse events should be phoned / faxed / e-mailed to Abbott EP. within 24 hours of learning of an event. The following information will be collected and recorded as appropriate.

- Nature of adverse event
- Date of onset of adverse event
- Date of resolution of adverse event, if applicable
- Statement as to why it is considered unanticipated, if applicable
- Statement as to why it is considered serious, if applicable
- Statement as to the degree to which it is considered device related, and why
- Results of any diagnostic tests that were performed
- Description of any treatment administered

It is the responsibility of each Investigator to report all Serious Adverse Events and/or Serious Adverse Device Effects to the Ethics Committee, according to national regulations and Ethics Committee requirements.

Abbott EP will assure that the Authorized Representative will report all Serious Adverse Events to the Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations.

Any protocol modifications deemed necessary by this review will be reported to the EC and, for sites located outside of Europe, to the applicable Ministry of Health.

10.3 ANTICIPATED ADVERSE EVENTS

Table 8 – Anticipated Adverse Events

Description	Description
Discomfort due to insertion/removal of vascular sheaths beyond what is normally observed	Ventricular arrhythmia requiring defibrillation
Hemorrhage and/or hematoma at sheath insertion requiring evacuation or transfusion	Cardiac tamponade due to perforation
Extremity weakness, swelling, and/or pain	
Discomfort and/or damage to the skin, muscles, or nerves due to remaining in a supine position for an extended period of time.	Nerve injury (diaphragmatic paralysis, pyloric spasm, gastric hypomotility)
Complete AV block	Air embolism

Nausea /vomiting	Allergic reaction
Headache different from baseline	Endocarditis
Hypertension >180 mm Hg systolic (repeated measures)	Esophageal-atria fistula
Hypotension <80 mm Hg systolic (repeated measures)	Hemothorax
Brief "black out" periods	Pericarditis
Shortness of breath/Dyspnea	Pseudo aneurysm
Feeling of chest pain, skipped beats, and/or rapid heart rate different from baseline	Pulmonary vein stenosis
Damage to skin from prolonged exposure to x-rays	Radiation injury
New arrhythmias (not previously documented)	Renal failure form IV contrast
Arterial injury requiring intervention	Respiratory failure
Thromboembolism	Stroke/TIA
Local/systemic infection	Valvular damage
Pneumothorax	Pleural effusion
AV fistula	Pulmonary edema
Thrombophlebitis	Anemia requiring transfusion
Pulmonary embolism	Vasovagal reaction
Myocardial infarction	New pericardial effusion >1 cm
Discomfort and/or damage to the skin, muscles, or nerves due to percutaneous access in excess of usual	Death **(must be reported within the regulation of serious adverse events)**
Left heart access via trans-septal puncture has known potential adverse events of: cardiac perforation, cardiac tamponade, and embolic events*.	

* Literature reviews have demonstrated that the risk of such events are <1%. Mullins, Charles E. "Trans-septal left heart catheterization: Experience with a new technique in 520 pediatric and adult subjects." Pediatric Cardiology, v. 4, pgs. 239-246 (1983).

10.4 DEVICE DEFICIENCIES AND MALFUNCTIONS

Investigators must report all possible device deficiencies or malfunctions associated with the device per institutional standard practice and regulations. This includes unexpected outcomes or device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

- **Definitions**
  - Device deficiency - inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling (EN ISO/FDIS 14155:2010).
  - Malfunction - failure of an investigational medical device to perform in accordance with its intended purpose when used in

accordance with the instructions for use (EN ISO/FDIS 14155:2010).

11 INVESTIGATOR REQUIREMENTS

11.1 PROTOCOL ADHERENCE

Each Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol before seeking approval from the EC or CA. Each Investigator will be responsible for enrolling only those subjects who have met all of the protocol inclusion criteria and none of the exclusion criteria.

11.2 ELECTRONIC CASE REPORT FORMS AND DATA CAPTURE SYSTEM

Data collection will involve the use of the Electronic Data Capture (EDC) system, to which only authorized personnel will have access. Electronic case report forms will be used to capture study data in an EDC system. Entering of eCRFs should be handled in accordance with instructions from the Sponsor or Sponsor representative. All eCRFs must be completed by qualified study center personnel. Each Investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor via the system, providing missing or corrected data, approving all changes performed on the subject data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

Queries may be issued electronically to the study site and answered electronically by that site's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) will be collected.

11.3 SOURCE DOCUMENT MAINTENANCE

Source documents may include, but are not limited to, study progress notes, study- or subject-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. The original signed ICF for each participating subject shall be filed with records kept by the Investigator. All documents produced in this study will be maintained by the Investigator and made available for inspection by the Sponsor or Sponsor representative and applicable regulatory authorities.

11.4 STUDY MONITORING REQUIREMENTS

The Sponsor or Sponsor representative will conduct site visits to inspect study data, subjects' medical records, and eCRFs in accordance with current ICH E6 Good Clinical Practice (GCP) guidelines, and the respective United

States or foreign regulations and guidelines, as applicable. The Sponsor or Sponsor representative will also be able to review query status remotely, which may warrant additional communication with the Investigator and the study site's personnel. The Investigator will make available to the Sponsor, or Sponsor representative, source documents, signed ICFs, and all other study-related documents. The Investigator will allow the Sponsor or Sponsor representative and applicable regulatory authorities to inspect facilities and records relevant to this study.

11.5 STUDY COMPLETION

The Sponsor requires the following data and materials before a study can be considered complete or terminated, including, but not limited to:

- Laboratory findings, clinical data, and all special test results from screening through FU
- eCRFs properly completed by appropriate study personnel and signed and dated by the Investigator within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.
- Copies of complete device accountability records, if applicable
- Copies of all or CA approvals and acknowledgements
- A summary of the study prepared by the Investigator (an EC or CA summary letter is acceptable)

12 STUDY MANAGEMENT

Study management will occur in accordance with ISO 14155, (Clinical investigation of medical devices for human subjects – Good clinical practices), the Declaration of Helsinki, the applicable national regulations and Institutional research policies and procedures. Several key components of study management are discussed separately below.

12.1 EC OR COMPETENT AUTHORITY APPROVAL

The EC or CA must approve the protocol or amended protocol (if applicable) and the corresponding ICF before the study may be initiated; any recruiting materials before use; and subsequent amended protocols and corresponding ICFs before instituting amendment-specified changes to the study, unless required for subject safety.

The Investigator is responsible for informing the EC or CA of any changes made to the protocol, and to advise the EC or CA, at least once a year, about the progress of the study. The Investigator (or Sponsor, if applicable) is also responsible for notifying the EC or CA of any significant AEs that occur during the study according to local EC or CA requirements.

- **Study Registration**

The study will be registered with www.clinicaltrials.gov in accordance with the Declaration of Helsinki.

12.2 MONITORING

The study will be monitored periodically at each enrolling site at not less than
3-month intervals for the purposes of

- Verifying compliance to the protocol and applicable regulations,
- Verifying case report form data to original entries in source files,
- Abbott EP employees or representatives will monitor the study according to company standard operating procedures.

12.3 STUDY AUDITS

The Sponsor and representatives of regulatory health authorities are permitted to inspect the study documents (protocol, case report forms, study-related medical records, study correspondence with EC and sponsor, etc.). In addition to ongoing monitoring of the study, GCP audits by the

Sponsor or its representatives are also permitted. All attempts will be made to preserve subject confidentiality.

12.4 PROTOCOL DEVIATIONS

A protocol deviation is defined as any event where the clinical investigator or site personnel did not conduct the study according to the protocol.

Investigators can only initiate deviations from the protocol where necessary to protect the life or physical well being of a subject, i.e., in an emergency. Protocol deviations shall be reported to the Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor, or taken to protect the subject in an emergency. Subject-specific deviations will be reported on the eCRF. Non-subject specific deviations, (e.g., unauthorized use of an study device by a physician who has not signed an investigator agreement, etc.), will also need to be reported to the Sponsor. All deviations, regardless of major / minor or pre-approved, will be reported on the eCRF. Investigators will also adhere to procedures for reporting study deviations to their EC in accordance with their specific EC reporting policies and procedures.

Regulations require that investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

- **Definitions**

For reporting purposes, the Sponsor classifies study deviations as major or minor:

- Major deviation: Any deviation from subject inclusion and exclusion criteria; subject informed consent procedures (e.g., failure to obtain informed consent or failure to obtain informed consent prior to study entry); randomization errors; failure to report SAE's, unanticipated adverse device effects, and deaths within applicable regulatory timeframes; device accountability issues (e.g., missing or lost investigational product); or device misuse / unauthorized device use.

- Minor deviation: Deviation from a protocol requirement such as incomplete/ inadequate subject testing procedures, non-compliance with medication regimens, follow-ups performed outside specified time windows, etc.

The Sponsor will monitor continuously monitor site compliance. The site will receive a list of site-specific study deviations on an annual basis as part of the Annual Progress Report and as part of the Final Report upon completion of the study.

12.5 DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee (DMC) will provide ongoing independent review and adjudication of study endpoint events, the safety data, further ensuring the continued safety of subjects, as well as the validity and scientific merit of the trials. The DMC consists of at least three voting members, with relevant expertise. The DMC members are not directly related to the study.

13 DEVICE ACCOUNTABILITY

All medical devices used in this clinical study carry a CE mark and will be used within their intended use. Therefore, this study does not require a dedicated device accountability procedure. The investigator shall maintain adequate records of the receipt and disposition of all devices per local institutional standard practice and regulations.

14 PROTECTION OF HUMAN SUBJECTS

14.1 STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the current ICH E6 GCP, the ethical principles of the Declaration of Helsinki, current FDA GCP guidelines, and any additional national or EC or CA-required procedures, whichever represents the greater protection for the individual.

14.2 INFORMED CONSENT

This study will be conducted in compliance with current ICH E6 GCP pertaining to informed consent. To participate in the study, the subject must sign and date the ICF after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits, before initiation of any study-related procedures. A copy of the signed ICF must be provided to the subject. If applicable, the ICF will be provided in certified translation for non-English-speaking subjects. Signed ICFs must remain in the subjects' study files and be available for verification by the Sponsor or Sponsor representative at any time.

15 STATISTICAL CONSIDERATIONS

15.1 GENERAL ANALYSIS PRINCIPLES

All primary endpoint analyses will be conducted under the principle of "Intention-To-Treat" (ITT), where each subject randomized to a treatment group who has had a mapping and/or ablation catheter inserted shall be considered part of the ITT group. As a secondary exploratory analysis, a "Per Protocol" (PP) analysis may be performed with a subgroup of the ITT group who have no major protocol deviations reported.

15.2 STUDY ENDPOINTS

A. Long-Term Effectiveness (Primary effectiveness endpoint)

The primary effectiveness endpoint is single-procedure freedom from AF/AT recurrence from 3-12 months after the index AF ablation procedure (with 90-day blanking period).

The hypothesis to be tested is the recurrence rate for FIRM-guided AF ablation is not inferior to that experienced by the conventional AF ablation arm.
The statistical hypothesis for this endpoint is operationalized as follows:

H_0: $\delta > .15$

H_A: $\delta < .15$

$\alpha = .05$ (two-tailed)

Where:

$\delta = p_C - p_F$

p_C = Proportion free from AF recurrence at twelve (12) months post index ablation procedure for the conventional AF ablation arm (.50)

p_F = Proportion free from AF recurrence at twelve (12) months post index ablation procedure for the FIRM-guided AF ablation arm (.55)

The non-inferiority margin for this hypothesis is 15% (.15). If the lower limit of the two-sided 95% confidence interval calculated for the difference in proportions (δ) is less than .15, the null hypothesis will be rejected and evidence in favor of the alternative (FIRM-guided ablation for atrial fibrillation is not inferior to conventional ablation for atrial fibrillation) affirmed.

This non-inferiority margin was chosen based on that used in the FreezeAF[3] and VGLB[4] trials.

[3] Luik, Armin MD, et. al. (2010). Rationale and design of the FreezeAF trial: A randomized controlled noninferiority trial comparing isolation of the pulmonary veins with the cryoballoon catheter versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation. American Heart Journal. 159(4):555-560.

The proportion of successes in each treatment arm shall be estimated using Kaplan-Meier survival estimation.

B. **Acute Effectiveness (Secondary effectiveness endpoint)**

The acute success of each arm shall be determined by:

1. A subject in the FIRM-guided ablation arm shall be classified as an acute success upon elimination of all identified atrial fibrillation rotors.
2. A subject in the conventional ablation arm shall be classified as an acute success upon isolation of all pulmonary veins.

The proportion of successes in each arm will be calculated as follows:

$$\frac{n}{N}$$

Where:

n = the total count of "successful" subjects in the arm in question

N = the total count of subjects for that arm in the ITT group

The statistical hypothesis for this endpoint is operationalized as follows:

H_O: $p_F = p_C$

H_A: $p_F \neq p_C$

$\alpha = .05$ (two-tailed)

Where:

p_F = the proportion of "successes" in the FIRM-guided ablation arm

p_C = the proportion of "successes" in the conventional ablation control arm

The analysis to be performed for this endpoint will be a Chi-square test of Independence.

C. **Long-Term Secondary Safety (safety endpoint)**

Long-term safety is defined as freedom from serious adverse events related to the procedure (including those related to repeat procedures) within one year of the index procedure.

[4] Dukkipati,, Srinivas R. MD, et. al. (2015). Pulmonary Vein Isolation Using the Visually Guided Laser Balloon. Journal of the American College of Cardiology. 66(12):1350-1360.

The statistical hypothesis for this endpoint is operationalized as follows:

H_O: $p_F = p_C$

H_A: $p_F \neq p_C$

$\alpha = .05$ (two-tailed)

Where:

P_F = the proportion of subjects free from serious adverse events related to the procedure (including those related to repeat procedures) within one year of the index procedure in the FIRM-guided ablation arm

p_C = the proportion of subjects free from serious adverse events related to the procedure (including those related to repeat procedures) within one year of the index procedure in the conventional ablation control arm

The proportion of successes in each treatment arm shall be estimated using Kaplan-Meier survival estimation.

D. **Acute Safety (Secondary safety endpoint)**

The acute safety success of either treatment arm is defined as freedom from serious adverse events related to the procedure within seven (7) days of the index procedure.

The proportion of successes in each arm will be calculated as follows:

$$\frac{n}{N}$$

Where:

n = the total count of subjects presenting freedom from serious adverse events related to the procedure within seven (7) days of the index procedure.

N = the total count of subjects in that arm in the ITT group

The statistical hypothesis for this endpoint is operationalized as follows:

H_O: $p_F = p_C$

H_A: $p_F \neq p_C$

$\alpha = .05$ (two-tailed)

Where:

P_F = the proportion of "successes" in the FIRM-guided ablation arm

p_C = the proportion of "successes" in the conventional ablation control arm

The analysis to be performed for this endpoint will be a Chi-square test of Independence.

E. **Additional Secondary Investigations**

Secondary Endpoints (unpowered) include:

1. AF termination or CL prolongation, as identified by:
   a. Termination of spontaneous or induced AF by ablation of the source of arrhythmia.
   b. Reduction of the mean AF rate by at least 10% by ablation of the source of arrhythmia.
2. Single-procedure freedom from AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period) (Long-Term Effectiveness).
3. Freedom from symptomatic AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period).
4. Freedom from AF recurrence from 0 – 12 months post index ablation procedure (without 90-day blanking period) (Long-Term Effectiveness).
5. Freedom from AF recurrence at 12 months post index ablation procedure (can include repeat procedures) (Long-Term Effectiveness).

Additional Investigations (unpowered) include:

1. Total RF ablation time.
2. Total Radiation Exposure.
3. Repeat ablation procedure and associated hospitalizations.
4. Quality of Life, as measured by the EQ-5D and AFEQT.
5. Cost-effectiveness analysis.

15.3 POWER AND SAMPLE SIZE ESTIMATION

Since the primary objective of this study relates to the long-term effectiveness of FIRM-guided ablation versus conventional ablation for atrial fibrillation (AF), power and sample size estimates have been calculated relative to that endpoint only. We anticipate enrolling 77 subjects in each treatment arm, plus an additional 8 subjects per arm to account for possible drop-outs / lost to follow-ups, for a total of 170 subjects (in approximately 20 sites).

Description	**Assumptions**
FIRM Group Freedom from recurrence of AF at 3 months	.55
CONVENTIONAL Group Freedom from recurrence of AF at 3 months	.50
Probability of Type I error (α) (two-sided test)	.05
Minimum Total Sample Size (includes 10% adjustment for drop-outs and losses to follow-up)	170 (85 per group)

With 77 subjects in each group, the lower limit of the observed one-sided 95.0% confidence interval will be expected to exceed -0.150 with 80% power when the Standard proportion, p_C, is 0.500 and the Test expected proportion, p_E, is 0.550; results are based on 1000 simulations using the Newcombe-Wilson score method to construct the confidence interval. In order to account for potential drop-outs and losses to follow-up, an additional 10% (16) will be added to the total sample size, for a final sample size of 170 (85 per group).[5]

This power and sample size calculation was performed using NQuery 7.0 on the Microsoft Windows 10 operating system.

[5] Newcombe RG (1988) Interval estimation for the difference between independent proportions: comparison of eleven methods. Statistics in Medicine 17:873-890.

16 PUBLICATION POLICY

The data generated in this clinical study are the property of the Sponsor and are confidential. As the study Sponsor, Abbott retains the first right to disclose the results of the Study through a publication such as the ICMJE or any other public disclosure 12 months after the close-out of the last study center. A Publication Steering Committee (PSC) may be formulated to oversee the publication process. The PSC may include Principal Investigator(s), members of the Steering Committee, investigators and other individuals who have expertise in the area and employees of Abbott. All manuscripts and abstracts will be reviewed and approved by the PSC and/or Abbott. Authorship on the primary publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.