Randomized Evaluation of Redo Ablation Procedures of Atrial Fibrillation with Focal Impulse and Rotor Modulation Guided Procedures (Redo-FIRM)

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Sponsor: Abbott Electrophysiology (Topera, Inc.)
645 Almanor Avenue
Sunnyvale, CA 94085

Regional Principal Investigators:

Europe:

[redacted]

North America:

[redacted]

Medical Monitor: [redacted]

Study Management: [redacted]

[redacted]

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1 PROTOCOL SIGNATURE PAGE

Protocol: Redo-FIRM

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:

[redacted]

2 ABBREVIATIONS and DEFINITIONS

ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life questionnaire
ASD	Atrial septal defect
AT	Atrial tachycardia
CABG	Coronary artery bypass graft (surgery)
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Event Committee
CFAE	Complex fractionated atrial electrograms
$CHADS_2$	Scoring system in determining stroke risk for those with AF
CIED	Cardiac implanted electronic device
CRA	Clinical Research Associate
e-CRF	Electronic Case Report Form
CT	Computed tomography
CTI	Cavotriscuspid isthmus
DSMB	Data and Safety Monitoring Board
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 echocardiogram
TTE	Transthoracic echocardiogram
TIA	Transient ischemic attack
UADE	Unanticipated Adverse Device Effect

3 PROTOCOL SYNOPSIS

Sponsor: Abbott Electrophysiology (Topera, Inc.)
Protocol Title: Randomized Evaluation of Redo Ablation Procedures of Atrial Fibrillation with Focal Impulse and Rotor Modulation Guided Procedures (REDO-FIRM)
Planned Study Centers: Up to 30 centers in Europe and North America
Primary Objective: Evaluate the safety and effectiveness of FIRM-guided procedures in conventional repeat ("redo") RF ablation for the treatment of paroxysmal and persistent atrial fibrillation. **Secondary/Additional Objectives:** • Evaluate the acute effectiveness of FIRM-guided procedures in eliminating the source of arrhythmia. • Quality of life outcomes. • Paroxysmal and persistent AF outcomes. • Post-ablation inducibility. • Health economic outcomes.
Study Design: This is a prospective, multicenter, randomized study to assess the safety and effectiveness of FIRM-guided procedures in conventional "redo" RF ablation for the treatment of persistent and paroxysmal atrial fibrillation.
Sample Size: A total of 268 subjects will be enrolled and equally (1:1) randomized.
Randomization: FIRM + PVI vs. PVI+ (after confirming PVI reconnection by Lasso).

Ablation Procedure:
• FIRM + (Re-) PVI vs (Re-)PVI+
• Optional ablation:
  • FIRM group: prophylactic ablation* of the RA-Isthmus line and any inherent arrhythmia that is found to have focal firing during procedure.
  • Control group: ablation of any arrhythmia that is found to have focal firing during procedure/that is provoked. The following prophylactic ablation* may be performed:
  ▪ RA-isthmus line
  ▪ Non PV-trigger (if provoked)
  ▪ Caval vein isolation
• No LA appendage isolation.
• **Prophylactic ablation should be performed for all study subjects if it is the standard of practice of the Investigator.*

Study Assessments & Follow-Up: • Patient informed consent • Screening/Baseline

[redacted]

Follow-Up Assessments: • 10 days post procedure for safety assessment. • 6 weeks post procedure prior to blanking period exit. • 3, 6, and 12 months with 7 days of continuous monitoring within 1-2 weeks of each follow-up visit. Blanking period is 8 weeks post-procedure. Cardioversion may be done around week 6 to have patients exit blanking period. Amiodarone discontinuation: 4-6 weeks prior to procedure; 4-6 weeks post-procedure or follow standard practice. Antiarrhythmic drug, Class IC: Discontinue after 5 half-lives.
Inclusion Criteria: Subjects are required to meet the following inclusion criteria: 1. Male or female 18 – 80 years of age. 2. Has at least one (1) episode of spontaneous persistent or paroxysmal atrial fibrillation documented by rhythm strip/ECG following the most recent ablation. 3. Had one (1) previous AF ablation after January 01, 2013, but NOT within the last 3 months. 4. Oral anticoagulation required with either Novel Oral Anticoagulant (NOAC) or Warfarin (in the case of Warfarin, therapeutic INR ≥ 2.0 for at least three weeks prior to randomization) for those subjects who meet two or more of the following criteria: a. Age 65 years or older b. Diabetes c. Coronary artery disease (CAD) d. Congestive heart failure e. Hypertension with systolic>165 mm Hg 5. Willingness and able to remain on anti-coagulation therapy for a minimum of 3 months post procedure for all subjects and at least 12 months post procedure if the patient is on anti-coagulation pre-procedure or has $CHADS_2$ score ≥ 2 (or CHADs-Vasc score >1). 6. Left atrial diameter < 6.0 cm via transthoracic echo or transesophageal echo; or <6.5 cm via CT or MRI up to 6 months pre-procedure with documented image of largest dimension, or intra-procedural ICE or atrial angiogram if CT/MRI not available. 7. Willingness, ability and commitment to participate in baseline and follow-up evaluations without participation in another clinical trial which may confound the results of this study, unless approved by the Sponsor. 8. Informed consent in writing from patient.

[redacted]

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:
        - Coronary artery bypass surgery (CABG) within the last six months, or
        - 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 IV.
3. Ejection fraction < 35% (within previous 6 months).
4. Previous AF ablation within the last 3 months.
5. ASD closure device, LAA closure device, prosthetic mitral or tricuspid valve, or permanent pacemaker.
6. History of myocardial infarction (MI) within the past three (3) months.
7. Contraindication to Heparin and Warfarin/other novel oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban).
8. Diagnosed atrial myxoma.
9. Any concomitant arrhythmia or therapy that could interfere with the interpretation of the results from this study.
10. Untreatable allergy to contrast media.
11. Severe electrolyte abnormalities at time of the ablation procedure or atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible non-cardiac cause.
12. Atrial fibrillation from a reversible cause (e.g., surgery, hyperthyroidism, pericarditis).
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. Any history of a cerebrovascular disease (including stroke or TIA) within the past 6 months.
17. Any anticipation of cardiac transplantation or other cardiac surgery within the next 12 months.
18. 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.
19. Acute illness or active systemic infection or sepsis.
20. Any history of blood clotting abnormalities or bleeding abnormalities.
21. Life expectancy of less than 12 months.
22. Any Intramural thrombus, tumor, or other abnormality that precludes catheter introduction or safe manipulation.

[redacted]

23. Women known to be pregnant.
Safety Assessments: Safety shall be evaluated both acute (in hospital) and long term: • Freedom from serious adverse events related to the procedure within 10 days of the procedure. • Freedom from procedure-related serious adverse events (including from any repeat procedures required) within one year of the procedure.
Effectiveness Assessments: • Acute Effectiveness The acute success of FIRM-guided procedure is defined as elimination of the source of arrhythmia identified by FIRMap as indicated by: 1. No evidence of the source on FIRMap immediately post-procedure, OR 2. Reduction of electrogram amplitude to <0.2mV in region designated by FIRMap. • Long-term Effectiveness The long-term effectiveness of FIRM-guided procedures versus conventional ablation shall be defined as: 1. Freedom from atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) recurrence at 3-12 months post procedure. Freedom from AF/AT/AFL recurrence is defined as no documented episodes > 30 seconds with conventional non-invasive 7-day monitoring. In the case of a cardiac implanted electronic device (CIED), freedom from AF/AT /AFL recurrence is defined as no documented episodes > 30 seconds in a 1-week window of the follow-up visits, in addition to any symptomatic episodes with documented episode > 30 seconds. AT recurrence does not include episodes of CTI (cavotricuspid isthmus) dependent flutter.

[redacted]

4 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 in the left atrium to isolate these veins. Such procedures take 3-5 hrs. to complete 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, Narayan et al[2] have developed an algorithm that has been licensed for use with a novel mapping technology (RhythmView, Abbott Electrophysiology (Topera, Inc.), Menlo Park, CA) 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.

[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.

[redacted]

Redo-FIRM is a prospective, multicenter, randomized, controlled study to assess the safety and effectiveness of FIRM procedures followed by ablation including PVI versus a standard conventional procedure including PVI for the redo-treatment of persistent or paroxysmal atrial fibrillation after 1 failed preview PVI.

4.1 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 2-3 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 50-70% 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.

4.2 HYPOTHESIS

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

5 STUDY OBJECTIVES

The primary objective is to evaluate the safety and effectiveness of FIRM-guided procedures in conventional repeat ablation for the treatment of persistent or paroxysmal atrial fibrillation (AF).

The secondary objectives are: 1) to evaluate the acute success of FIRM-guided procedure in eliminating the source of arrhythmias, and 2) to evaluate quality of life outcomes.

6 STUDY DESIGN

The study is designed as a prospective, multicenter, randomized, study to assess the safety and effectiveness of FIRM-guided repeat RF ablation procedure including PVI versus a standard PVI procedure for the treatment of persistent and paroxysmal atrial fibrillation.

6.1 SAMPLE SIZE

Up to 268 subjects at up to 30 investigative sites will be enrolled and equally (1:1) randomized between a cohort undergoing conventional RF ablation, vs. a cohort undergoing FIRM-guided conventional RF ablation. Additionally, ablation of any atrial tachycardias (AT) and/or the cavotricuspid isthmus may be performed in those subjects with documented AT/atrial flutter.

6.2 STUDY DURATION

Overall study duration (first subject enrolled through last subject exit) will be comprised of approximately 18 months of enrollment period, 1 month per subject for screening and baseline measurements, and 12 months per subject for follow-up, for a total study duration of up to 31 months. 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.

7 ENDPOINTS

7.1 PRIMARY EFFECTIVENESS ENDPOINTS

Effectiveness endpoints are defined in the table below.

Table 1 – Primary Effectiveness Endpoints

Endpoint	Definition
Long term success	The long-term effectiveness of FIRM-guided procedures versus conventional ablation shall be defined as: • Freedom from atrial fibrillation AF/AT/AFL recurrence at 3 -12 months post procedure. Freedom from AF/AT/AFL recurrence is defined as no documented episodes > 30 seconds with conventional non-invasive 7-day monitoring. In the case of a cardiac implanted electronic device (CIED), freedom from AF/AT/AFL recurrence is defined as no documented episodes > 30 seconds in a 1-week window at the follow-up visits, in addition to any symptomatic episodes with documented episode > 30 seconds. AT recurrence does not include episodes of CTI (cavotricuspid isthmus) dependent flutter.

7.2 PRIMARY SAFETY ENDPOINTS

Safety shall be evaluated both acute (in hospital) and long term, as defined in the table below.

Table 2 – Primary Safety Endpoints

Endpoint	Description
Acute success	Freedom from serious adverse events related to the procedure within 10 days of the procedure.
Long-term success	Freedom from procedure-related serious adverse events (including those related to repeat procedures) within one year of the initial procedure.

7.3 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.

[redacted]

Table 3 – Secondary Endpoints

Endpoint	Definition
Acute Effectiveness	The acute success of FIRM-guided procedure is defined as elimination of the source of arrhythmia identified by FIRMap as indicated by: 1. No evidence of the source on FIRMap immediately post-procedure, OR 2. Reduction of electrogram amplitude to <0.2mV in region designated by FIRMap.

Table 4 – Additional Evaluations

Parameter	Definition
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 compared between the FIRM-guided and conventional ablation groups. If ablation for AT/atrial flutter is pursued, this ablation time will be documented separately
Repeat procedure and hospitalization	Any descriptive information regarding repeat procedures and re-hospitalizations will be compared between groups
Cumulative long-term freedom from AF	Cumulative long-term freedom from AF will be assessed at 12 months after the initial AF procedure but will permit results of repeat ablation
Early Recurrence of AF/AT	Recurrences of sustained AF/AT in the first 8 weeks (blanking period).
Change in Atrial Function	Change in left atrial size and pulmonary vein inflow Doppler on echocardiogram (when available)
Change in Ventricular Function	Change in left ventricular ejection fraction and parameters of diastolic dysfunction (when available)
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 time points) 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.

[redacted]

8 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

8.1 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. Has at least one (1) episode of spontaneous persistent or paroxysmal atrial fibrillation documented by rhythm strip/ECG following the most recent ablation.
3. Had one (1) previous AF ablation after January 01, 2013, but NOT within the last 3 months. Detailed documentation of the previous ablation strategy is required.
4. Oral anticoagulation required with either Novel Oral Anticoagulant (NOAC) or Warfarin (in the case of Warfarin, therapeutic INR ≥ 2.0 for at least three weeks prior to randomization) for those subjects who meet two or more of the following criteria:
    a. Age 65 years or older
    b. Diabetes
    c. Coronary artery disease (CAD)
    d. Congestive heart failure
    e. Hypertension with systolic>165 mm Hg
5. Willingness and able to remain on anti-coagulation therapy for a minimum of 3 months post procedure for all subjects and at least 12 months post procedure if the subject is on anti-coagulation pre-procedure or has $CHADS_2$ score ≥ 2 (or CHADs-Vasc score >1).
6. Left atrial diameter < 6.0 cm via transthoracic echo; or <6.5 cm via CT or MRI up to 6 months pre-procedure with documented image of largest dimension, or intra-procedural ICE or atrial angiogram if CT/MRI not available.
7. Willingness, ability and commitment to participate in baseline and follow-up evaluations without participation in another clinical trial which may confound the results of this study, unless approved by the Sponsor.
8. Signed informed consent.

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:
        - Coronary artery bypass surgery (CABG) within the last six months, or
        - 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 IV.

[redacted]

3. Ejection fraction < 35% (within previous 6 months).
4. Previous AF ablation within the last 3 months.
5. ASD closure device, LAA closure device, prosthetic mitral or tricuspid valve, or permanent pacemaker.
6. History of myocardial infarction (MI) within the past three (3) months.
7. Contraindication to Heparin and Warfarin/other novel oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban).
8. Diagnosed atrial myxoma.
9. Any concomitant arrhythmia or therapy that could interfere with the interpretation of the results from this study.
10. Untreatable allergy to contrast media.
11. Severe electrolyte abnormalities at time of the ablation procedure or atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible non-cardiac cause.
12. Atrial fibrillation from a reversible cause (e.g., surgery, hyperthyroidism, pericarditis).
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. Any history of a cerebrovascular disease (including stroke or TIA) within the past 6 months.
17. Any anticipation of cardiac transplantation or other cardiac surgery within the next 12 months.
18. 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.
19. Acute illness or active systemic infection or sepsis.
20. Any history of blood clotting abnormalities or bleeding abnormalities.
21. Life expectancy of less than 12 months.
22. Any Intramural thrombus, tumor, or other abnormality that precludes catheter introduction or safe manipulation.
23. Women known to be pregnant.

8.2 INFORMED CONSENT

The investigator will obtain written informed consent from the subject using the IRB/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.

8.3 MOMENT OF ENROLLMENT

The subject will be considered "enrolled" in the study after the subject has signed the study informed consent form, completed all baseline assessments, and randomized to a study treatment group. Randomization will occur on the day of the procedure.

Optional sub-study cohort enrollment: If the patient is disqualified on the day of the procedure because PV reconnection cannot be confirmed, the patient cannot be randomized / enrolled in the study. However, if AF can be sustained the patient may undergo FIRM-guided ablation and enroll in the sub-study cohort. The patient will be required to comply to all protocol follow-up requirements. See Section 10.2b.

8.4 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.

8.5 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.

9 INVESTIGATOR SELECTION

9.1 INVESTIGATIVE SITES

A. Up to 30 investigational sites in Europe and North America will participate in this study

B. 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 FIRM maps produced by the system.
- Participated in 5 FIRM-guided procedures prior to enrolling any subjects in the study.

9.2 EQUIPMENT REQUIREMENT

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

- 64-pole mapping catheter (Topera FIRMap Catheter) and appropriate analyzer to acquire full chamber data (RA or LA) per Topera RhythmView system requirements.
- Topera 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.

9.3 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 IRB/EC requirements, or insufficient recruitment of study subjects.

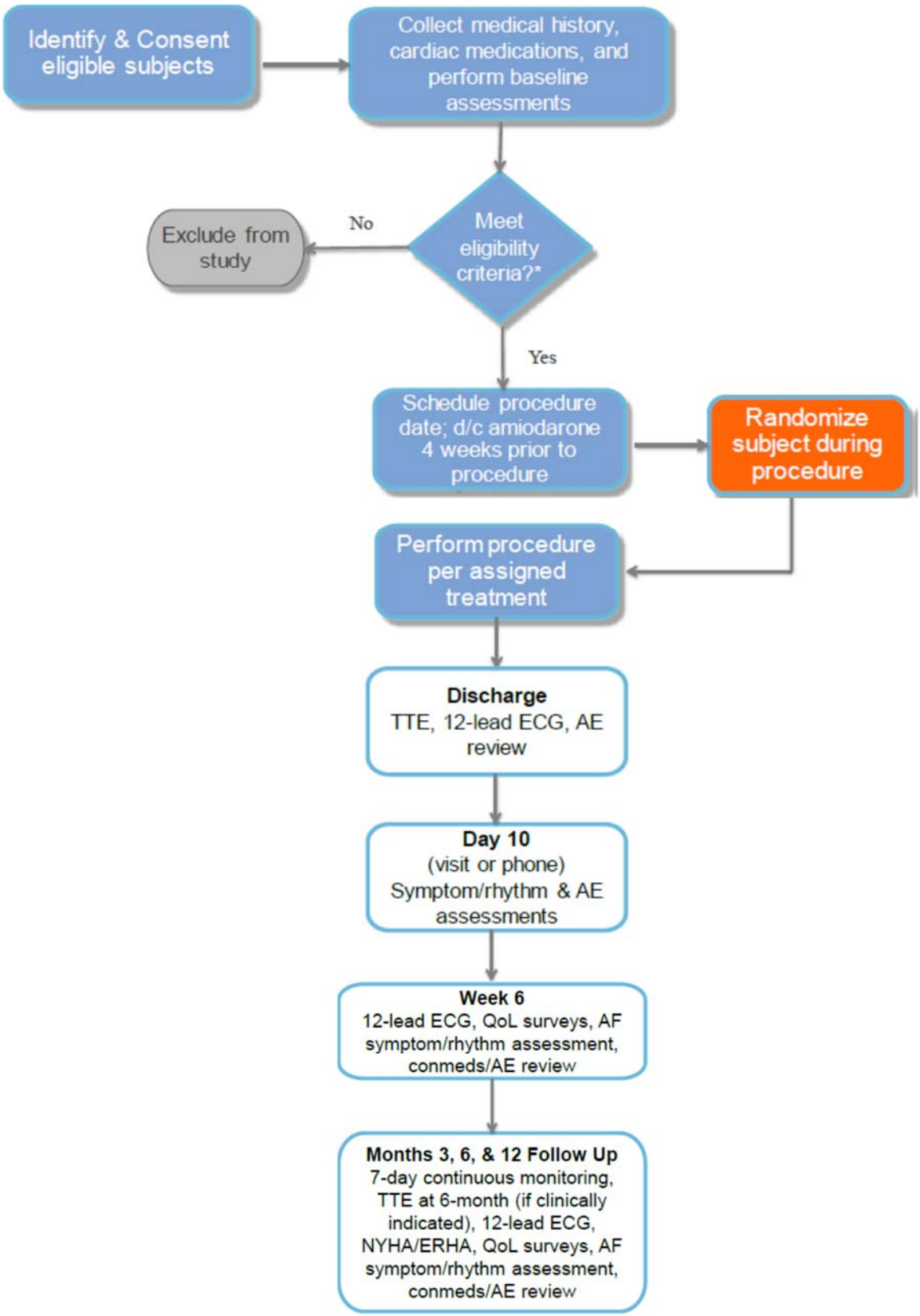
10 STUDY FLOW AND VISIT SCHEDULE

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 Chart



[redacted]

Table 5 – Schedule of Assessments

Event	Baseline	Procedure	Discharge	Day 10	6-week	3-month	6-month	12-month	Unscheduled
Informed Consent	✪								
Demographics, Medical history, Cardiac diagnosis	✪								
Lab work per standard of care (including HCG for women of childbearing potential)	✪								
INR if patient is on Warfarin (as appropriate on post-procedure f/u)	✪				✪	✪	✪	✪	▩
TEE[1]	▩								▩
TTE[2]	▩		✪				▩		▩
Diagnostic 12-lead ECG	✪		✪		✪	✪	✪	✪	▩
Documentation of AF	✪								▩
Concomitant cardiac medications	✪				✪	✪	✪	✪	▩
NYHA and ERHA Class Assessment	✪					✪	✪	✪	▩
EQ-5D QoL Survey	✪				✪	✪	✪	✪	▩
AFEQT QoL Survey	✪				✪	✪	✪	✪	▩
AF Symptom and rhythm assessment	✪		✪	✪(☎)	✪	✪	✪	✪	▩
AE review		✪	✪	✪(☎)	✪	✪	✪	✪	▩
7-day ambulatory continuous ECG monitor						✪	✪	✪	▩
AF interventional procedures performed (repeat ablation, AF-related hospitalization)				▩	▩	▩	▩	▩	▩

[1] TEE will be performed at baseline if clinically indicated.
[2] TTE is required at Discharge. TTE will be performed at baseline and at 6-month follow-up, if clinically indicated.

Legend: ✪ = Required ☎= via Telephone ▩ = if applicable

[redacted]

10.1 SCREENING AND BASELINE

A. *Screening*

Patients at the investigational sites with persistent or 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 based on 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.
- 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 1 episode of persistent or paroxysmal atrial fibrillation (AF) documented by rhythm strip/ECG following the most recent ablation..
- 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 and ERHA class assessment.
- Current cardiac rhythm.
- Largest dimension left atrial diameter measured from transthoracic echo, cardiac CT or cardiac MR within the last 6 months 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 6 months or from the pre-procedure TEE or TTE.
- When clinically indicated, TEE will be performed 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.

- 12-Lead ECG within 72 hours of study procedure.
- Cardiac medications currently prescribed for the subject's daily medical therapy.
- Pre- procedure Laboratory values per standard practice.
- 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, subjects fitting the investigator's standard criteria for anticoagulation will have been orally anti-coagulated (in case of Warfarin, with therapeutic INR (≥2.0) for at least three weeks prior to randomization, or they may be placed on therapeutic doses of subcutaneous low-molecular-weight heparin (LMWH)). As dictated by center clinical practice, oral anti-coagulation will be discontinued and either subcutaneous LMWH or IV heparin will be substituted at therapeutic doses until the time of the procedure. At the investigator's discretion, dabigatran, rivaroxaban or apixaban will be withheld for 24 hours prior to the procedure.
- Amiodarone to be discontinued 4 weeks prior to procedure.
- Antiarrhythmic drug, Class IC: Discontinue after 5 half-lives.
- EQ-5D and AFEQT Quality of Life surveys.
- Pregnancy test to be performed for women of child bearing potential

Each site will maintain a screening log noting the reasons for screening failures.

10.2 STUDY PROCEDURE

The individual center and investigator should define the ablation strategy for the conventional redo-procedures of the Control group prior to participation in the trial.

- Ablation guidelines (optional):
  - **FIRM group**: prophylactic ablation* may be performed for the RA-Isthmus line and for any inherent arrhythmia that is found to have focal firing during the procedure.

  - **Control group**: additional ablation may be performed for any arrhythmia that is found to have focal firing during procedure. The following prophylactic ablation* may be performed:
    - RA-isthmus line
    - Non PV-trigger (if provoked)
    - Caval vein isolation

    **Prophylactic ablation should be performed for all study subjects if it is determined to be the standard of practice of the Investigator.*

  - LA appendage isolation are not permitted.

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. The insertion of the

FIRMap catheter or performing transseptal puncture, whichever comes first, will be followed immediately by an IV heparin bolus, followed by repeated heparin administration, adjusted as necessary to achieve and maintain an ACT above 300 seconds.

B. ***Intra-procedure***

Subject randomization will be performed during the procedure after the following criteria are met. See Figure 2.

1) AF is sustained for at least 5 minutes uninterrupted.
2) Confirmation of PV reconnection.

IMPORTANT:

- If AF cannot be sustained and PV reconnection cannot be confirmed, the patient is disqualified and cannot be randomized / enrolled in the study. The patient will undergo conventional AF ablation at the discretion of the investigator.
- If the patient is in sinus rhythm and one or more of his/her veins are not isolated, it is acceptable to isolate the vein(s) before induction of AF. AF must still be sustained for 5 minutes before the patient can be randomized. If AF cannot be sustained after re-isolation of veins, the patient will be excluded from study before randomization.
- **Optional sub-cohort enrollment**: If AF can be sustained but PV reconnection cannot be confirmed, the patient is disqualified and cannot not be randomized / enrolled in the study. However, the patient may undergo FIRM-guided ablation and enroll in the sub-study cohort. The patient will be required to comply to all protocol follow-up requirements.

Figure 2.

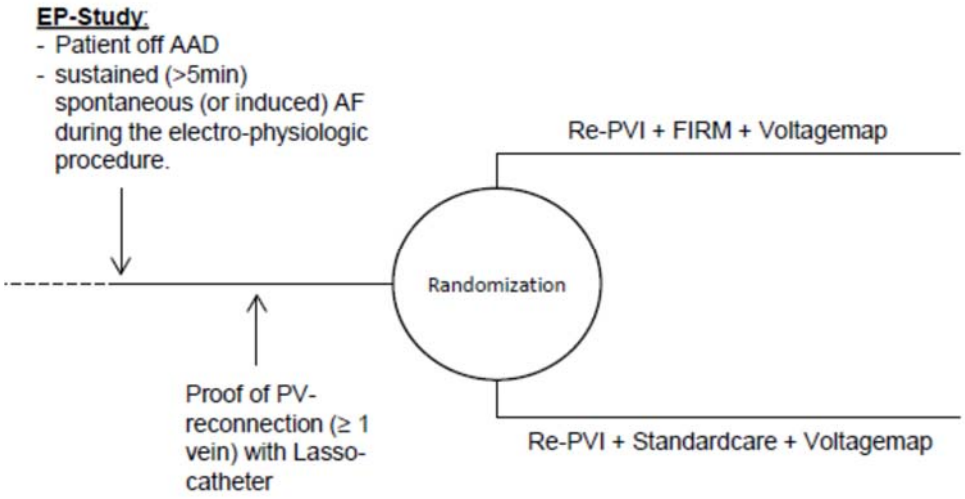


Table 6 – Intra-Procedure Guidelines

During the procedure, the following steps should be taken.

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.
1. Induction of sustained AF	Burst pacing at 200 ms for 5 s from the RA and twice from the CS.
2. Induction of non PV-Triggers (if standard care includes ablation of extra-pulmonary foci)	A non-PV trigger is defined as a PAC that triggers either sustained or non-sustained AF or atrial tachyarrhythmia (AT). Repetitive PACs that do not result in sustained or non-sustained AF/AT are <u>not</u> considered non-PV triggers. Reproducible AF/AT initiation is required for non-PV triggers to allow for accurate mapping of the region of origin outside the PVs with multi polar catheters with or without 3D mapping systems. Non-PV triggers will be induced as follows: 1. Isoproterenol infusion (starting at 2 mcg and incrementing up to 20 mcg per standard laboratory protocol). Per standard laboratory protocol, another sympathomimetic agent (e.g., IV norepinephrine or epinephrine) may be substituted for isoproterenol. 2. Cardioversion of spontaneous AF or AF induced by left or right atrial rapid pacing. AF and the subsequent cardioversion may be induced/ performed during infusion of isoproterenol so as to maximize the possibility of inducing AF triggers. As part of the trigger protocol, multiple cardioversions may be necessary whenever AF is induced (spontaneously or with isoproterenol infusion / burst pacing) with the endpoint of mapping the trigger beat(s) leading to post-cardioversion early AF recurrence. In case of early AF recurrence, the beat initiating AF will be considered a trigger and will be analyzed for site of origin using the mapping techniques described in the definition.
PV reconnection	Look for PV reconnection (at least one vein) with Lasso catheter.
Randomization	The patient will be randomized once PV reconnection is confirmed and AF is sustained > 5 minutes.
Reference catheter placement	Reference catheters (including 64-pole FIRMap catheter(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 according to the institution's standard practice.
Anticoagulation	Upon insertion of 64-pole FIRMap catheter or transseptal puncture (whichever comes first), an IV heparin bolus should be administered, followed by repeated heparin administration, adjusted as necessary to achieve and maintain an ACT above 300 sec. ACT will be monitored every 10 minutes following initial heparin delivery until the target value is achieved and subsequently checked at least every thirty minutes during the procedure.

[redacted]

Catheter placement	Catheters may be inserted and used according to the institution's standard practice.
Source arrhythmia diagnosis	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 Topera RhythmView® system. 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 or Nav-X systems for documentation of anatomy and ablation lesion locations.
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).
Conventional Ablation	In the conventional arm of the study, data will be recorded regarding any additional ablation such as that performed per local routine for AF (e.g. additional trigger elimination).
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.
Vascular access sheath removal	The vascular access sheaths will be removed when the ACT reaches a clinically acceptable level.
Voltage mapping	Perform voltage mapping is strongly recommended.

The following precautions should be taken per standard of practice:

- Typically, in order to reduce the risk of introducing air emboli through a trans-septal 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; and
    - The time multiple sheaths cross the septum may be minimized.
- Just prior to ablation, at each ablation site in the posterior LA or 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***

Table 7.

Data	Description
Fluoroscopy times	To be recorded: *Total fluoroscopy time* • The total fluoroscopy time for the procedure (a.k.a., "pedal down" time) *Ablation fluoroscopy time* • The time between the first ablation catheter insertion to last ablation catheter removal from the left atrium.
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 catheters.
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.
- Once the sheaths have been removed and hemostasis has been achieved, heparin or LMWH will be restarted along with oral anticoagulation (warfarin or novel oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban)).

  The platelet inhibitor (if administered during the procedure) and heparin or LMWH will be continued until the INR exceeds 2.0 (in the case of warfarin use for longer-term oral anticoagulation).

  Oral anti-coagulation will continue for at least three months after the procedure. Subjects who were on oral anticoagulation pre-procedure will be maintained on anticoagulation for the duration of the study.

  Note: Oral Glycoprotein IIb/IIIa Inhibitors use is discouraged during the follow-up period.

- Post-procedure drug therapy will include re-initiation and/or continuation of any pre-procedure cardiac medications including all anti-arrhythmic drugs used for the treatment of atrial flutter or other arrhythmias/cardiac diseases. 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 either via a Cardiac Implanted Electronic Device (CIED) with interrogation at intervals per protocol or all subjects without CIED will receive a 7-day continuous event monitor at 3, 6, and 12 months post-procedure. If AF symptoms are documented as recurrent AF within the follow-up period, further treatment shall be at the discretion of the physician (e.g., drugs, re-ablation, etc.).

- Pre-discharge evaluation will include:
  - Diagnostic 12-lead ECG
  - Echocardiography
  - Symptom and rhythm assessment
  - Antiarrhythmic medications
  - Adverse events

10.3 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 8 Follow-up (FU) Visit Windows

Visit	Allowed Visit Date Range
Day 10 (Phone or visit)	±2 days
6 weeks	± 1 week
3 months	± 1 week
6 months	± 2 weeks
12 months	± 4 weeks

[redacted]

- ***Resolution Period***

Following ablation treatment, subjects will undergo 8-week "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. Cardioversion may be done around week 6 to have patients exit blanking period.

Note: During the 8-week 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***

Amiodarone must be discontinued 4-6 weeks prior to ablation and may be re-administered after ablation by the discretion of the investigator. Antiarrhythmic drug, Class IC: must be discontinued (5 half-lives.) prior to ablation and can be re-administered after ablation by the discretion of the investigator.

- ***Recurrence of AF***

If re-ablation for AF 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 10 Follow-up (±2 days)***

(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. ***Six-Week Follow-up (±1 week)***

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- EQ-5D and AFEQT Quality of Life surveys
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation
- In case of atrial fibrillation electric cardioversion within 4 weeks

C. ***Three-Month Follow-up (±1 week)***

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- 7-day continuous ECG monitor or CIED interrogation
- EQ-5D and AFEQT Quality of Life surveys
- Symptom and rhythm assessment

- Concomitant anti-arrhythmic medications
- Adverse event documentation

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

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- 7-day continuous ECG monitor or CIED interrogation
- Echocardiography, if clinically indicated
- EQ-5D and AFEQT Quality of Life surveys
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation

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

The following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- 7-day continuous ECG monitor or CIED interrogation
- EQ-5D and AFEQT Quality of Life surveys
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse event documentation

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

The following assessments/procedures will be performed, if possible:

- Diagnostic 12-lead ECG
- 7-day continuous ECG monitor or CIED interrogation by the discretion of the operator
- EQ-5D and AFEQT Quality of Life surveys
- Symptom and rhythm assessment
- Concomitant anti-arrhythmic medications
- Adverse Event documentation

11 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.

11.1 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.

- **Adverse Device Effect (ADE)** – Adverse Event related to the use of a medical device. This includes:
    - Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.
    - Any event that is a result of a use error or intentional misuse.
- **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

[redacted]

- 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:
- Pre-planned 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. For example, repeat ablation for recurrence of AF would not be considered an SAE.
- 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.

- **Serious Adverse Device Effect (SADE)** – Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
- **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.

11.2 ADVERSE EVENT EVALUATION AND REPORTING

- ***AE Reporting***

Conditions or diseases which are pre-existing and chronic should not be recorded as adverse events. 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 unifying 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).

- ***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 Abbott EP (Topera) Medical Monitor and will also be reviewed during quarterly DSMB meeting.

- ***SAE Reporting***

All serious adverse events (SA(D)Es) should be phoned / faxed / e-mailed to Abbott EP (Topera, Inc.) 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 IRB/EC, according to national regulations and IRB/EC requirements.

Abbott EP (Topera Inc.) 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 IRB/EC and, for sites located outside of Europe, to the applicable Ministry of Health.

11.3 ANTICIPATED ADVERSE EVENTS

Table 9 – 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).

11.4 DEVICE DEFICIENCIES AND MALFUNCTIONS

Investigators must report all possible device deficiencies, malfunctions or near incidents 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 or protocol (EN ISO/FDIS 14155:2010).

12 INVESTIGATOR REQUIREMENTS

12.1 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 IRB/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.

12.2 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 (eCRFs) 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.

12.3 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.

12.4 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

[redacted]

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.

12.5 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 IRB/IEC or CA approvals and acknowledgements
- A summary of the study prepared by the Investigator (an IRB/IEC or CA summary letter is acceptable)

13 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.

13.1 IRB/IEC OR COMPETENT AUTHORITY APPROVAL

The IRB/IEC 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 IRB/IEC or CA of any changes made to the protocol, and to advise the IRB/IEC 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 IRB/IEC or CA of any significant AEs that occur during the study according to local IRB/IEC or CA requirements.

- **Study Registration**

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

13.2 MONITORING

The study will be monitored periodically at each enrolling site per the study monitoring plan 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 (Topera) employees or representatives will monitor the study according to company standard operating procedures.

13.3 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 [redacted]

13.4 PROTOCOL DEVIATIONS

[redacted]

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 wellbeing 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 a 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 IRB/EC in accordance with their specific IRB/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 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.

13.5 DATA MONITORING COMMITTEE

A Data Monitoring Committee [DMC] will provide ongoing independent review of the 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.

14 DEVICE ACCOUNTABILITY

The investigator shall maintain adequate records of the receipt and disposition of all devices per local institutional procedure and regulations.

15 PROTECTION OF HUMAN SUBJECTS

15.1 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 IRB/IEC or CA-required procedures, whichever represents the greater protection for the individual.

15.2 INFORMED CONSENT

This study will be conducted in compliance with current ICH E6 GCP pertaining to informed consent, the current CFR (Title 21, Parts 50). 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.

16 STATISTICAL CONSIDERATIONS

16.1 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 met all inclusion/exclusion criteria and 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, and have achieved their 12-month visit (endpoint).

16.2 Study Endpoints

A. Long-Term Effectiveness (Primary effectiveness endpoint)

Single Repeat Procedure Freedom from AF/AT/AFL recurrence* in the period from 3 to 12 months after the initial AF ablation procedure.

Freedom from AF/AT/AFL recurrence is defined as no documented episodes > 30 seconds with conventional non-invasive 7-day continuous monitoring. In the case of a cardiac implanted electronic device (CIED), freedom from AF/AT/AFL recurrence is defined as no documented episodes > 30 in a 1-week window at the follow-up visits, in addition to any symptomatic episodes with documented episode > 30 seconds. AT recurrence does not include episodes of CTI (cavotricuspid isthmus) dependent flutter.

The statistical hypothesis for this endpoint is operationalized as follows:

H_O: $p_E = p_C$
H_A: $p_E \neq p_C$
$\alpha = .05$ (two-tailed)

Where:

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

The proportion of successes in each treatment arm shall be evaluated relative to their respective primary endpoint using both Chi-Square (Binomial, 1df) and by Kaplan-Meier survival estimation. Each evaluation will include 95% confidence intervals.

B. Acute Effectiveness (Secondary effectiveness endpoint)

The acute success of FIRM-guided procedure is defined as elimination of the source of arrhythmias identified by FIRMap as indicated by;

1. No evidence of the source on FIRMap immediately post-procedure, OR

2. Reduction of electrogram amplitude to <0.2mV in region designated by FIRMap

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: $p_E = p_C$
H_A: $p_E \neq p_C$
α = .05 (two-tailed)

Where:

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

This endpoint will be evaluated using a Chi-Square test of independence, the proportions assumed to be binomial for each group.

C. Acute Safety (Primary safety endpoint)

The acute safety success of either treatment arm is defined as freedom from serious adverse events related to the procedure within ten (10) 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 ten (10) 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: $p_E = p_C$
H_A: $p_E \neq p_C$
α = .05 (two-tailed)

Where:

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

This endpoint will be evaluated using a Chi-Square test of independence, the proportions assumed to be binomial for each group.

D. Long-Term Safety (Primary safety endpoint)

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

The statistical hypothesis for this endpoint is operationalized as follows:

H_O: $p_E = p_C$
H_A: $p_E \neq p_C$
$\alpha = .05$ (two-tailed)

Where:

p_E = the proportion of subjects free from serious adverse events related to the procedure (including from any repeat procedures required) within one year of the index procedure in the FIRM arm

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

The proportion of events in each treatment arm shall be evaluated relative to their respective primary endpoint using both Chi-Square (Binomial, 1df) and by Kaplan-Meier survival estimation. Each evaluation will include 95% confidence intervals.

16.3 POWER AND SAMPLE SIZE ESTIMATION

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17 PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the Sponsor and are [redacted] As the study Sponsor, Abbott retains the first right to disclose the results of the Study through a publication or any other public disclosure. 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.