Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT04244396
PerAF APAC
Persistent Atrial Fibrillation (Asia Pacific) Observational Study
Study Document No: ABT-CIP-10295
Version B
Date: 29-JUN-2020

Sponsor

Abbott
5050 Nathan Lane North
Plymouth, MN 55442
USA

[redacted]

Clinical Investigation Plan

[redacted]
PerAF APAC
Persistent AF (Asia Pacific) Observational Study

Version Letter:	[redacted]
Date:	June 29, 2020
Planned Number of Sites and Regions:	Up to 15 in South Korea, Singapore, Hong Kong, Taiwan, India, and other Asia Pacific countries as deemed necessary
Clinical Investigation Type:	Prospective, single arm, non-randomized, observational, multi-center clinical investigation.
Sponsor:	Abbott [redacted]
CIP Author of Current Version:	[redacted]

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator:

Printed name:
Signature:
Date:

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812 and OUS ISO14155:2011) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, PMDA, MHRA, etc.).

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1.0 INTRODUCTION

This clinical investigation is intended to collect safety and effectiveness information for the TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™ (TactiCath SE) for use in cardiac electrophysiological mapping and for the treatment of drug-refractory, recurrent symptomatic persistent atrial fibrillation (AF) when used in conjunction with a compatible radiofrequency (RF) generator and three-dimensional mapping system. This clinical investigation will be a post-market observational study and is intended to generate additional clinical evidence for the TactiCath SE ablation catheter for the treatment of drug refractory, symptomatic persistent atrial fibrillation in the Asia Pacific (APAC) region. Approximately one hundred (100) subjects will be enrolled at up to 15 sites in South Korea, Singapore, Hong Kong, Taiwan, India, and other Asia Pacific countries as deemed necessary. This clinical investigation is sponsored by Abbott and will be conducted in accordance with this clinical investigation plan (CIP). All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

Based on epidemiological studies of mainly North American and European populations, an estimated 20.9 million men and 12.6 million women suffer from AF.[1] The prevalence of AF is lower in Asians than in Westerners and is estimated to be approximately 0.7-1.1% in Asians older than 40. Despite this apparent difference in prevalence, the burden of AF in the Asia Pacific region is expected to become far greater than that in Western regions based on the increasing age and size of populations within the Asia Pacific regions.[2,3]

AF is a result of multiple diseases and mechanisms that are not completely understood and will often exacerbate an underlying heart condition. AF occurs when structural and/or electrophysiological abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation.[4] Symptoms associated with AF include fatigue, palpitations, dyspnea, hypotension, syncope, and heart failure. AF often progresses from paroxysmal to persistent over a variable period of time. Patients with persistent AF have worse outcomes than for patients with paroxysmal AF and are more likely to develop potentially life-threatening problems, such as stroke, tachycardia-induced cardiomyopathy and congestive heart failure, all of which may increase mortality.[5,6] Maintenance of sinus rhythm may confer a mortality benefit and is associated with improvements in symptoms and quality of life.

Management of patients with AF has traditionally consisted of three main components: (1) anticoagulation for stroke prevention; (2) rate control; and (3) rhythm control.[7] Persistent symptoms associated with AF remain the most compelling indication for a rhythm-control strategy. The efficacy of radiofrequency catheter ablation for maintaining sinus rhythm is superior to current antiarrhythmic drug therapy in select patient populations.[4] The decision whether to pursue catheter ablation depends on a large number of variables, including the type of AF, degree of symptoms, presence of structural heart disease, candidacy for alternative options such as rate control or antiarrhythmic drug therapy, likelihood of complications, and patient preference.[4] Catheter ablation is considered a reasonable indication for patients with symptomatic persistent AF refractory or intolerant to at least one Class I or III antiarrhythmic medication.[4,7] Catheter ablation may also be considered as first-line therapy in select patients before a trial of antiarrhythmic drug therapy when a rhythm-control strategy is desired.[4,7]

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The method of catheter ablation for persistent AF remains controversial.[5,7] The strategy for ablation is often individualized based on patient characteristics, atrial fibrillation history and coexisting structural heart disease. Electrical isolation of the pulmonary veins by catheter ablation is the cornerstone for most AF ablation procedures as most triggers for AF originate from the pulmonary veins.[6] Pulmonary vein (PV) isolation involves creating circumferential lesions around the veins to electrically isolate them from the rest of the left atrium. Additional non-PV ablation strategies are also often employed in patients with persistent AF to improve outcome and may consist of the following: ablation of the posterior wall of the left atrium; creating linear ablation lesions in the right or left atrium; mapping and ablation of areas of abnormal myocardial tissue; ablation of complex fractionated atrial electrograms or rotational activity; and/or ablation of autonomic ganglia.[7] These additional non-pulmonary vein ablation strategies all have a Class IIb recommendation (benefit of AF ablation is greater or equal to the risks and AF ablation may be considered) based on a moderate quality of evidence for these approaches.

Contact force sensing ablation catheter systems are a technology that is growing in adoption for AF ablation. Contact force sensing catheter systems provide feedback to operators regarding the force applied by the catheter tip on the cardiac wall. Recommendations for contact force catheters for atrial fibrillation ablation procedures are also defined in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus on AF Ablation (Class IIa recommendation, Level of evidence C).[7]

The TactiCath family of contact force sensing catheters have been studied extensively. The earlier generation TactiCath catheters were investigated in the TOCCATA[8], EFFICAS I[9] and II[10], and TOCCASTAR[11] clinical trials. The next generation, TactiCath Quartz, implemented an updated contact force sensing mechanism, which was studied in the TOCCASTAR Supplemental Clinical Study. Long-term follow up data are currently being collected in the TactiCath Quartz Post Approval Study. These clinical trials have investigated the safety and effectiveness of the previous generations of the TactiCath ablation catheters for the treatment of drug refractory, symptomatic AF.[8-11]

The TactiCath SE ablation catheter is the latest TactiCath contact force sensing catheter from Abbott, which incorporates a magnetic sensor for tracking with the EnSite Precision Mapping System and utilizes a new handle and shaft to improve catheter handling. Preclinical testing has demonstrated that the TactiCath SE ablation catheter has an acceptable safety profile. Additionally, the ongoing TactiSense IDE trial evaluating the paroxysmal AF population currently being conducted in the United States, Europe, and Australia, as well as the Persist-End IDE trial evaluating the safety and effectiveness of this catheter in the persistent AF population that is being conducted in the United States and Australia, have demonstrated acceptable safety profiles as of the date of this document.

The PerAF APAC trial is a prospective, single arm, non-randomized, observational, post-market clinical investigation to primarily evaluate the effectiveness of ablation with the TactiCath SE catheter for the treatment of drug refractory, symptomatic persistent AF in the Asia-Pacific population. Additionally, the PerAF APAC study will be used as supplemental data to the Persist-End clinical trial being conducted in the United States and Australia.

1.1.2 Rationale for Conducting this Clinical Investigation

The PERSIST-END investigational device exemption (IDE) clinical investigation currently being conducted by Abbott will be used to obtain regulatory approval from the Food and Drug Administration (FDA) for a persistent AF indication on the TactiCath™ catheter (TactiCath™ Contact Force Ablation Catheter, Sensor Enabled). Supplemental data obtained in the PerAF APAC trial will be used in conjunction with the Persist-End data to expand the paroxysmal AF indication to include a persistent AF indication in China and other Asia Pacific countries as needed.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

The objective of this clinical trial is to collect safety and effectiveness data for the TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™ (TactiCath SE) in the APAC patient population for the treatment of drug refractory, symptomatic persistent atrial fibrillation when following standard electrophysiology mapping and radiofrequency (RF) ablation procedures.

2.2 Devices to be Used in the Clinical Investigation

2.2.1 Name of the Device Under Investigation

All devices used in this clinical investigation must have proper regulatory approval and will be used according to their indications and Instructions for Use (IFU). The devices that will be used in this clinical study are all manufactured by St. Jude Medical and are summarized in **Table 1.**

TactiCath SE is commercially available in the geographies that will be participating in this trial. Additional commercially available tools may be used in this clinical study per physician discretion and per device IFUs unless specifically prohibited as described in this CIP.

Table 1. Devices to be Used in PerAF APAC Trial

Device Name	Model/Type	Region/Country
EnSite™ System (Amplifier and Display Workstation)	EE3000 EE3300	India South Korea Singapore Taiwan Hong Kong Thailand
EnSite Precision Software v2.2 or equivalent	H702496	
Ensite Precision Module, Sensor Enabled Kit	H702470 H702473 H702475	
EnSite Contact Force Module, v2.0 or later	H702500	
TactiCath Ablation Catheter, Sensor Enabled, Software Installation	H702517	
Cool Point™ Pump, v24 or later	85784 (OUS) IBI 89003	
TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™	A-TCSE-D A-TCSE-F A-TCSE-J A-TCSE-DD A-TCSE-FF A-TCSE-JJ A-TCSE-DF A-TCSE-FJ	
TactiSys™ Quartz Equipment	PN-004 400	
Ampere™ RF Generator, v1.04 or later	H700489 (OUS)[1] H700495	
Sensor Enabled™ Diagnostic Catheter Cable	D-AVSE-CBL22 D-AVHD-DF16	
EnSite Precision™ Surface Electrode Kit	EN0020-P 100003331	

1. The model number in India for the Ampere generator is H700495.

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2.2.2 Indication for Use

The indications for use for each country participating in this trial are listed below.

Hong Kong, India, Singapore, and Thailand
The TactiCath Contact Force Ablation Catheter, Sensor Enabled, is indicated for use in cardiac electrophysiological mapping (stimulation and recording), and, when used in conjunction with a radiofrequency generator, for cardiac ablation of supraventricular arrhythmias in the right and left atrium, including atrial fibrillation.

Taiwan
The TactiCath Contact Force Ablation Catheter, Sensor Enabled is indicated for use in cardiac electrophysiological mapping (including stimulation and recording) and for the treatment of left and right atrial, supraventricular arrhythmias, including atrial fibrillation during a cardiac ablation procedure when used in conjunction with a compatible radiofrequency generator.

South Korea
A device that is intended to measure the ECG, cardiac ejection, etc. and to transmit signals that are necessary for recording of these. It is also used to deliver stimulation (pacing) and perform tissue ablation.

Operating Principle:
The TactiCath Contact Force Ablation Catheter, Sensor Enabled, is designed to facilitate electrophysiological mapping of the heart chambers and to transmit radiofrequency current to the catheter tip electrode for intracardiac purposes and when used in conjunction with a RF generator, for cardiac ablation of supraventricular arrhythmias in the right and left atrium, including atrial fibrillation.

2.2.3 Description of the Device Under Investigation

2.2.3.1 TactiCath Sensor Enabled Ablation Catheter

The TactiCath SE is designed to facilitate electrophysiological mapping of the heart chambers and to transmit RF current to the catheter tip electrode for intracardiac ablation purposes. The catheter is used in conjunction with a RF generator, an irrigation pump, and a dispersive pad (indifferent patch electrode) when ablating. TactiCath SE is compatible with introducers or sheaths with a minimum diameter of 8.5 F. TactiCath SE is a sterile, single use catheter with a 7.5 F shaft and an 8 F distal section. It is constructed of thermoplastic elastomer material and noble metal electrodes.

TactiCath SE has novel contact force and magnetic sensors. It has a fluid lumen connected to open conduits within a 6-hole tip electrode for saline irrigation during the ablation procedure (**Figure 1**). For both uni-directional (**Figure 2**) and bi-directional catheters (**Figure 3**), the tip curvature is manipulated by the control mechanism located on the handle at the catheter's proximal end. To adjust the curve of the distal tip on the uni-directional catheter, the thumb control located on the handle may be pushed or pulled. To adjust the curve of the distal tip on the bi-directional catheter, the actuator may be used to deflect the catheter in either direction. The catheter interfaces with standard recording equipment and a compatible RF generator via the TactiSys Quartz Equipment using the optical connector and 19-pin electrical connector on the catheter. The catheters are available in eight distal curve shapes.

Please refer to the IFU for additional information regarding the TactiCath SE device used in this clinical investigation.

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Figure 1. Exposed View of the TactiCath SE Tip

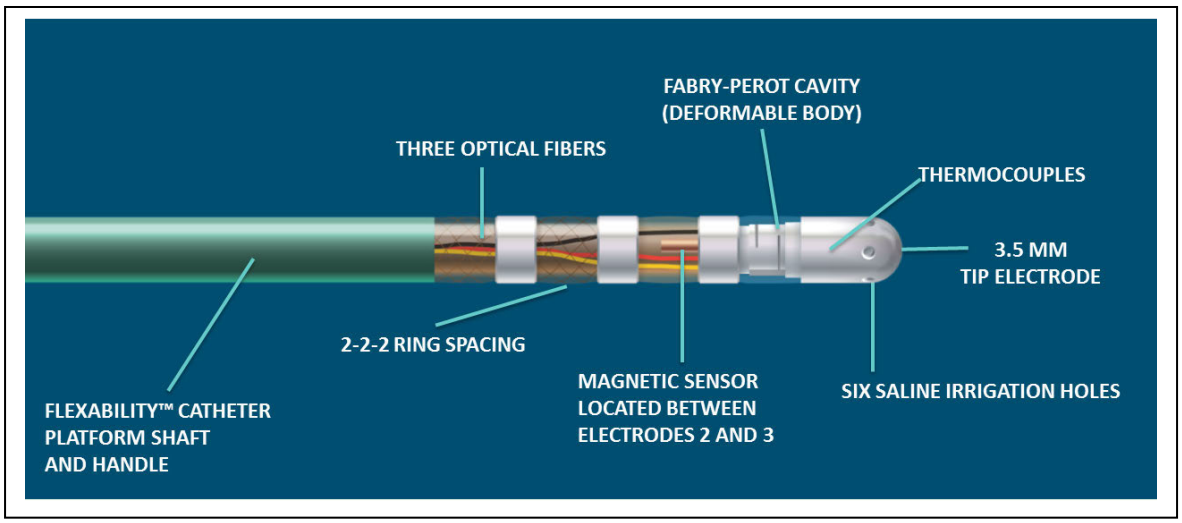


Figure 2. Uni-Directional TactiCath SE

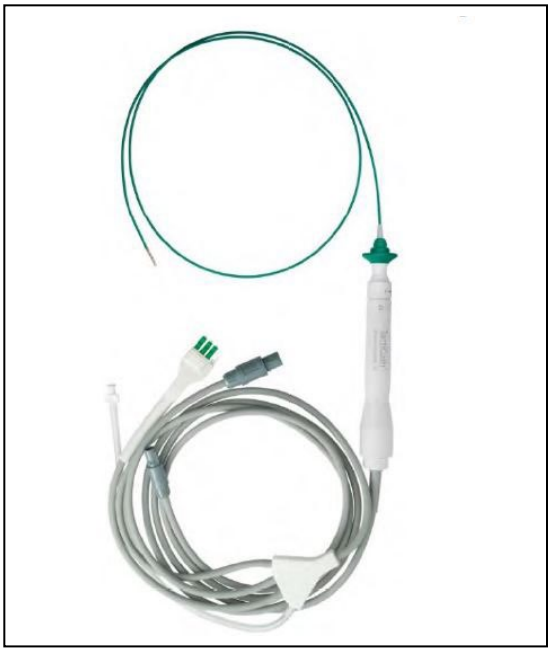
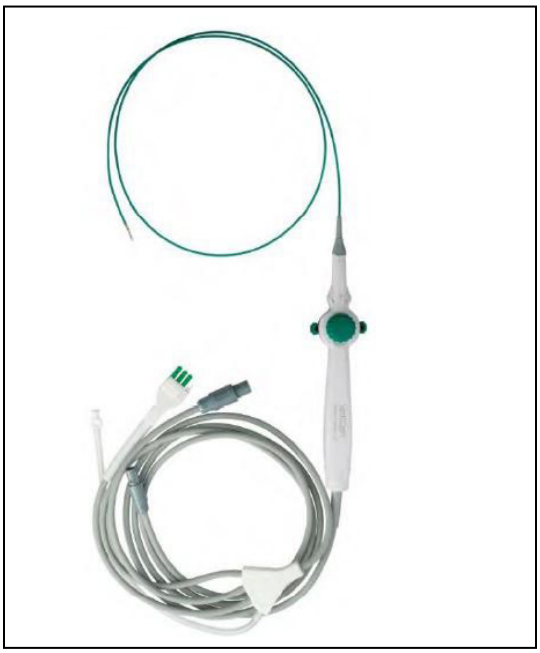


Figure 3. Bi-Directional TactiCath SE



2.2.4 Summary of Preclinical Studies

Preclinical testing has demonstrated that the TactiCath SE ablation catheter has an acceptable safety profile. Abbott has performed several preclinical studies evaluating TactiCath SE. A perfused porcine thigh study demonstrated that the TactiCath SE catheter and the TactiCath Quartz catheter show no statistical difference in the lesions created or observed adverse event rates at IFU recommended ablation conditions. A subacute intracardiac study compliant with Good Laboratory Practice (GLP) and a chronic intracardiac

GLP study were conducted to support safe delivery of the TactiCath SE ablation catheter to targeted locations within the heart and to create thermal lesions in atrial tissue. These studies were conducted in accordance with US 21 CFR Part 58, Good Laboratory Practice.

2.2.5 Device Handling

All devices will be used according to approved labeling and published medical practice guidelines. Regulations for handling of investigational devices do not apply.

3.0 CLINICAL INVESTIGATION DESIGN

The PerAF APAC trial is a prospective, single arm, non-randomized, observational, post-market clinical investigation using the TactiCath SE catheter for the treatment of drug refractory, symptomatic persistent AF in the APAC population. A core lab will independently assess AF/AFL/AT recurrence via Holter monitoring at the [redacted] follow-up visits. All serious adverse events (SAEs) will be independently adjudicated by qualified physicians not participating in the trial.

[redacted]

This clinical investigation has been designed to use market approved product per approved labeling and follow patients according to "standard of care" thus reducing any pain, discomfort, fear, and any other foreseeable risk. Refer to the Risk Analysis section (**Section 15.0**) of this clinical investigation plan for details.

3.1 Clinical Investigation Procedures and Follow-up Schedule

The visit schedule for subjects is shown in **Figure 4**. Subjects will be consented for the trial at baseline as specified in **Section 5.2.2**. Once eligibility is confirmed, the subject will undergo an ablation procedure for treatment of their persistent AF condition. A blanking period of 90-days will be employed after the initial ablation procedure, followed by a 90-day therapy consolidation period and then a 9-month evaluation period for a total of 15-months of follow-up. Medication adjustments, cardioversions, and one repeat ablation procedure may be performed in either the blanking or therapy consolidation periods. It is recommended that subjects are off all Class I or III antiarrhythmic drugs (AADs) after the blanking and/or therapy consolidation period. All follow-up assessments will occur in-person at the clinic after the procedure, with the exception of the 7-14 day follow-up visit. The 7-14 day follow-up visit may occur either in-person or by phone call. The scheduled follow-up visits will occur at 7-14 days post-procedure (phone call or in-person), and at 3-months, 6-months, 12-months, and 15-months. Subjects will be exited from the trial after completing their 15-month follow-up visit.

The flowchart and follow-up requirements for this clinical investigation are shown in **Figure 4** below.

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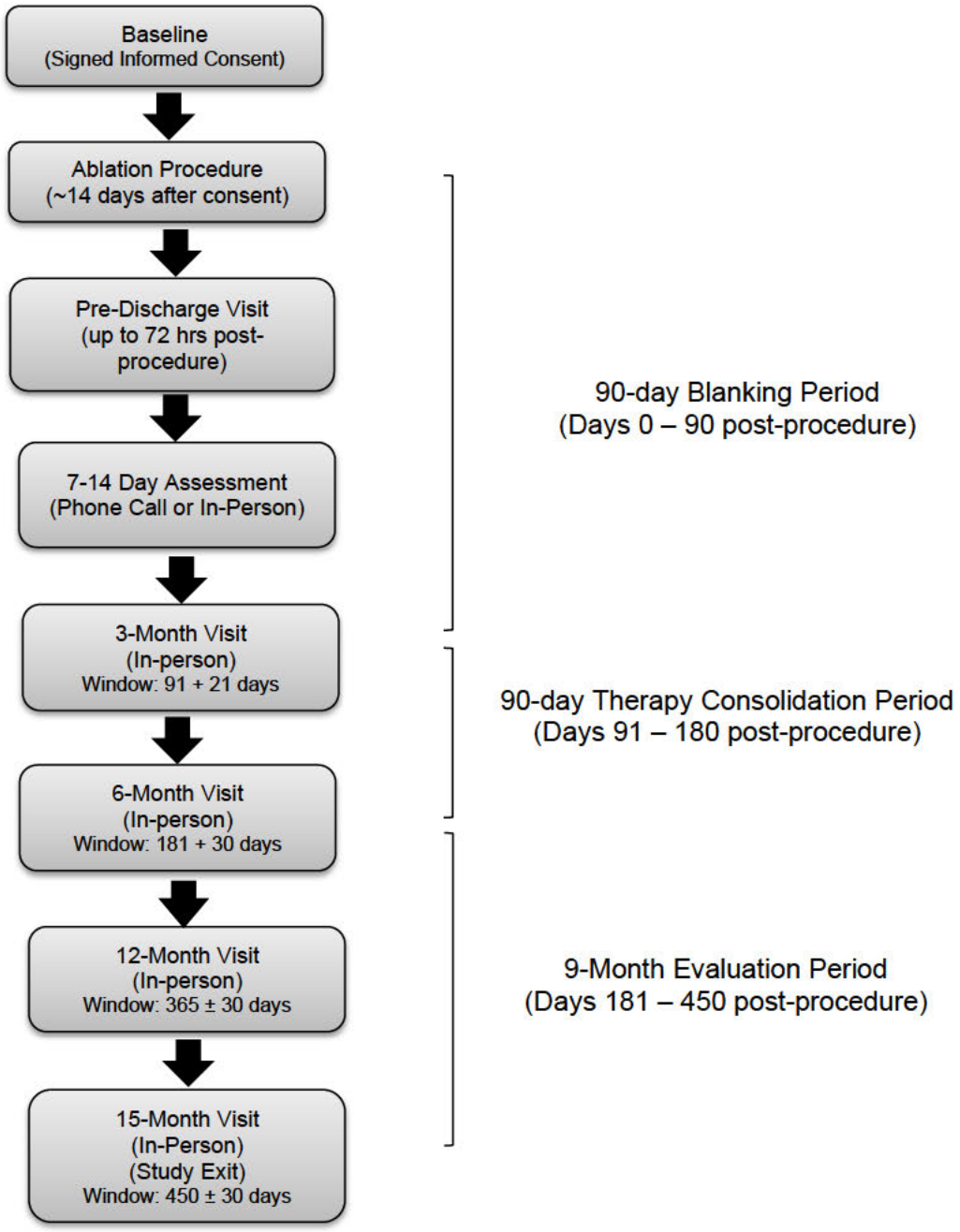
Figure 4. Study Flow Diagram



3.2 Measures Taken to Avoid and Minimize Bias

Multiple measures will be taken to avoid and minimize bias in this clinical investigation and are outlined below.

- PerAF APAC is a prospective clinical investigation in which the outcome is unknown at the time of enrollment
- All subjects must meet the defined eligibility criteria to minimize selection bias
- Guidance will be provided to sites regarding data collection for questionnaires
- Case report forms for data collection will be provided to sites, which will minimize inter-observer variability.
- Evaluation of the 6-month and 15-month Holter AF/AFL/AT recurrence data will be performed by an independent core laboratory.
- Adverse events will be independently adjudicated by qualified physicians.

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- A new unreasonable risk to the participating subjects has been identified such as an unanticipated increase in complaint rates related to the study.

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials to the Sponsor and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in **Section 11.5**.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate, and return patients to their standard medical treatment.

4.0 ENDPOINTS

Only non-powered endpoints will be assessed in this trial.

4.1.1 Primary Safety Endpoint and Rationale

The rate of device and/or procedure-related serious adverse events with onset within 7-days of any ablation procedure that uses the TactiCath SE catheter (initial or repeat procedure performed ≤180 days of initial procedure) that are defined below:

- Atrioesophageal fistula[1]
- Cardiac tamponade/perforation[1]

- Death
- Heart block
- Myocardial infarction (MI)
- Pericarditis[2]
- Phrenic nerve injury resulting in diaphragmatic paralysis
- Pneumothorax
- Pulmonary edema (respiratory insufficiency)
- Pulmonary vein stenosis[1]
- Stroke/cerebrovascular accident (CVA)
- Thromboembolism
- Transient ischemic attack
- Vascular access complications (including major bleeding events[3])

1. Atrioesophageal fistula, cardiac tamponade/perforation and pulmonary vein stenosis will be evaluated through 15-months.
2. Pericarditis is a common occurrence for almost all procedures and will only be considered a primary safety endpoint event if the pericarditis pleuritic symptoms last longer than 7-days and/or requires hospitalization of greater than 24 hours for reasons other than for observational purposes only.
3. Bleeding is a major complication of AF ablation if it requires and/or is treated with transfusion or results in a 20% or greater fall in hematocrit.

Definitions regarding these safety events are provided in **Appendix III**.

AF/AFL/AT recurrences that meet the definition of seriousness as noted in **Section 7.1.2** without coexisting conditions (e.g. thromboembolism, worsening heart failure, etc.) will be counted as effectiveness failures but will not contribute to this safety endpoint.

[redacted]

4.2 Additional Data

Additional data to be collected in this clinical investigation are described and will be reported using summary statistics. No hypothesis tests will be performed.

[redacted]

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects who have drug refractory, symptomatic, persistent AF. Subjects must provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Members of the site's clinical investigation team (physician and/or research coordinator, or other delegated and qualified personnel) previously trained to this CIP must screen potential patients for clinical investigation eligibility and document the screening effort onto a site-specific Screening Log. Patients who meet the inclusion criteria and none of the exclusion criteria may participate in this clinical investigation.

Patients presenting at clinical sites as potential subjects will be fully informed about the clinical investigation. Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin.

The following assessments may need to be performed after obtaining consent and prior to the procedure, as part of the screening process (further described in **Section 6**):

- Verification that a left atrial thrombus is not present on the day of or within one day of the ablation procedure
- Measurements for left ventricular ejection fraction (LVEF) and left atrial (LA) diameter if not performed in the 6-months prior to the ablation procedure, if not documented prior to consent, and/or is not standard of care at the site

Subject data will be collected following enrollment (subject is consented and has met all eligibility criteria) into the clinical investigation.

In the case in which a subject does not meet all inclusion criteria or meets one or more exclusion criteria that is discovered prior to insertion of the TactiCath SE catheter into their vasculature, the subject is considered a screen failure. The Principal Investigator or the delegated clinical investigation personnel will record the screen failure in the hospital records and on the Screening Log.

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5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical investigation. The subject shall be provided with the Informed Consent form separately that is written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

5.2.2.1 Special Circumstances for Informed Consent

The following individual populations will be excluded from participation in this clinical investigation:

- Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population.
- Individuals under the age of 18 or age of legal consent are excluded from the study population.
- Individuals unable to read or write are excluded from the study population.
- Pregnant or breastfeeding women are excluded from the study population.

All other aspects of the Informed Consent process should be in compliance with **Section 5.2.2**.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment of eligibility criteria is based on review of candidate medical records at the site, an interview with a candidate patient, and determination by the investigator. If the specific tests noted in **Section 5.2.1** (LVEF, LA diameter, and presence of thrombus) were not completed prior to obtaining consent, they

must be assessed before the subject has an ablation catheter inserted into their vasculature for an ablation procedure.

Patients must meet ALL of the inclusion criteria to be considered for this clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation.

5.3.2 Inclusion Criteria

1) Patient must provide written informed consent prior to any clinical investigation related procedure.
2) Documented symptomatic persistent AF, which is defined as continuous AF sustained beyond 7-days and less than 1-year that is documented by (1) a physician's note AND (2) a 24-hour Holter within 90-days prior to the procedure, showing continuous AF, OR (3) two electrocardiograms (from any form of rhythm monitoring) showing continuous AF, with electrocardiograms taken at least 7 days apart
3) Refractory or intolerant to at least one Class I or III antiarrhythmic drug (AAD) as evidenced by recurrent symptomatic AF
   Note: Intolerance is defined as unable, unwilling, or refusal to take Class I or III AADs.
4) Age 18 years or older
5) Able and willing to comply with all pre-, post-, and follow-up testing and requirements

5.3.3 Exclusion Criteria

1) Continuous AF > 12 months (longstanding persistent AF)
2) Previous left atrial surgical or catheter ablation for atrial fibrillation or a previous procedure that required an incision in the left atrium with resulting scar
3) Any cardiac procedure (surgical or percutaneous) within 90-days prior to the initial procedure
   NOTE: Diagnostic cardiac procedures in which no intervention, implant, or incision was made in the cardiac tissue are not considered a surgical or percutaneous cardiac procedure.
4) CABG surgery within the 6-months (180-days) prior to the initial procedure
5) Valvular cardiac surgical/percutaneous procedure (i.e. ventriculotomy, valve repair or replacement and/or presence of a prosthetic or mechanical valve)
6) Any carotid stenting or endarterectomy
7) Documented or known left atrial thrombus on imaging
8) Left atrial (LA) diameter > 50 mm (parasternal long axis view or by CT)
9) Left ventricular ejection fraction (LVEF) < 40%
10) Unable to take anticoagulation medication due to contraindication or intolerance
11) History of blood clotting or bleeding abnormalities
12) Myocardial infarction (MI), acute coronary syndrome, percutaneous coronary intervention (PCI) within the 3-months (90-days) prior to the initial procedure
13) Documented thromboembolic event (including TIA) within the 12-months (365 days) prior to the initial procedure
14) Rheumatic heart disease
15) Uncontrolled heart failure or NYHA functional class III or IV

16) Severe mitral regurgitation (regurgitant volume ≥ 60 mL/beat, regurgitant fraction ≥ 50%, and/or effective regurgitant orifice area ≥ 0.40cm^2)
17) Awaiting cardiac transplantation or other cardiac surgery within the 12-months (365 days) following the initial ablation procedure
18) Unstable angina at the time of the initial procedure
19) Acute illness or active systemic infection or sepsis
20) AF secondary to electrolyte imbalance, thyroid disease, acute alcohol intoxication, major surgical procedure in the preceding 3-months, or other reversible or non-cardiac cause
21) Diagnosed atrial myxoma
22) Presence of implanted implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D)
23) 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 chronic symptoms
24) Significant congenital anomaly or other anatomic or comorbid medical problem that in the opinion of the investigator would preclude enrollment in this study or compliance with the follow-up requirements or impact the scientific soundness of the clinical trial results
25) Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period
26) Enrollment in an investigational study evaluating another device, biologic, or drug that may interfere with this clinical investigation at the time of the initial procedure or within 30 days prior to the initial procedure
27) Presence of any condition that precludes appropriate vascular access or manipulation of catheter
28) Life expectancy less than 12-months
29) Body mass index > 40 kg/m^2
30) Known sensitivity to contrast media (if needed during the procedure) that cannot be controlled with pre-medication
31) Renal failure requiring dialysis
32) Presence of other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results
33) History of atriotomy or ventriotomy
34) Implanted endocardial left atrial appendage occlusion device

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent and meets all eligibility criteria.

If a TactiCath SE device is used for ablation on an enrolled subject who does not meet eligibility criteria for the trial, they will not be withdrawn from the trial, will be counted in the analysis population and will complete all follow-up requirements.

5.5 Subject Withdrawal

Each enrolled subject shall remain in the clinical investigation until completion of the required follow-up period. However, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Death
- Voluntary withdrawal
- Lost to follow-up (described below)
- Subject's following is terminated according to **Section 3.3**

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor as documented on the appropriate CRF. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once they are withdrawn from the clinical investigation, except for the status (deceased/alive). If a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, they will be followed by their regular physician per their standard of care.

If for any reason, the subject has the TactiCath SE inserted into their vasculature, but no ablation was performed, and the subject will not be rescheduled to receive another ablation procedure, the subject will be followed for 30-days to assess safety and then exited from the trial.

In the event that a subject does elect to withdraw from the trial, the site should make attempts to schedule the subject for a final visit. At this final follow-up visit, the subject will undergo assessments as outlined for an unscheduled visit (**Section 6.7.1**) if the visit does not coincide with a scheduled follow-up visit.

Withdrawn subjects count towards the total enrollment at the site and will not be replaced by enrolling additional subjects.

<u>Lost-to-Follow-up</u>

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, for each time an attempt was made to contact the subject:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter should be sent via registered mail to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits.
- If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with the general practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

[redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

The Principal Investigator is responsible for ensuring all clinical investigation data is collected as outlined in this CIP. Unless otherwise noted, it is recommended that the site follow standard of care for any activities not specifically stated in this CIP.

6.1 Baseline Clinical Assessments

The assessments listed below will be collected from each subject at the Baseline Visit. Information gathered at this visit will be used to verify eligibility of the subject for the trial.

- Documentation of the informed consent process as defined in **Section 5.2.2**
- Demographics
- Medical history, cardiac arrhythmia history, and documentation for the diagnosis of persistent AF
- Administration of a 24-hour Holter that must demonstrate 100% continuous AF within 90-days of the procedure OR documentation of 2 ECGs (from any form of rhythm monitoring) taken at least 7-days apart showing continuous AF

  NOTE: Repeat Holter assessments are not allowed if 100% continuous AF was not demonstrated on the first 24-hour Holter assessment. If artifact is present in the tracing, it can be disregarded when assessing for 100% continuous AF. All readable portions of the tracing should demonstrate continuous AF (non-sinus rhythm).
- AAD history, including maximum ineffective dosages and dosages not tolerated
  - Intolerance is defined as unable, unwilling, or refusal to take Class I or III AADs
- Anticoagulation drug usage
- Complete physical exam including 12-lead ECG, NYHA assessment, and CHA_2DS_2VASc score assessment
- Neurological assessment as recommended in the 2017 Consensus Statement[7]
- Echocardiography or CT results or equivalent imaging (LVEF and LA diameter assessments)

[redacted]

- Thrombus assessment must be performed as specified in **Section 6.2.6**.
- Administration of the EuroQol Five Dimensions Questionnaire (EQ-5D-5L) quality of life questionnaire as defined in **Section 6.7.1**
- Documentation of adverse events and protocol deviations that occur after consent and prior to the procedure

6.2 Peri-Procedural Considerations

6.2.1 Anticoagulation

The anticoagulation strategies from the 2017 Expert Consensus Statement on Catheter and Surgical Ablation for AF[7] for pre- and post-ablation are outlined below and are recommended to be followed for management of study subjects. However, **it is strongly recommended that a strategy of uninterrupted anti-coagulation be in place for peri-operative management**. All start and stop times of anticoagulants must be documented for the trial. Subjects who are taking coumadin or warfarin will have international normalized ratio (INR) values documented on the day of the procedure and after the drug is restarted after the ablation procedure.

Pre-ablation

- Patients who are therapeutically anticoagulated with warfarin, dabigatran or rivaroxaban prior to the ablation are recommended to have the ablation procedure performed without interruption of the anticoagulant.

- Patients anticoagulated with a novel oral anticoagulant (NOAC) prior to undergoing an AF ablation procedure may have one to two doses of the NOAC withheld prior to AF ablation with re-initiation of the NOAC post-ablation.

- Anticoagulation guidelines that pertain to cardioversion of AF should be adhered to in patients who present for an AF ablation procedure.

Post-ablation

- In patients who are not therapeutically anticoagulated prior to catheter ablation of AF and in whom warfarin will be used for anticoagulation post-ablation, low molecular weight heparin or intravenous heparin should be used as a bridge for initiation of systemic anticoagulation with warfarin following AF ablation.

- Systemic anticoagulation with warfarin or NOAC is recommended for at least 2-months post-ablation of AF. Systemic anticoagulation beyond 2-months post-ablation should be based on the patient's stroke risk profile (not on the perceived success or failure of the ablation procedure).

- In patients who have not been anticoagulated prior to catheter ablation of AF or in whom anticoagulation with a NOAC or warfarin has been interrupted prior to ablation, administration of a NOAC 3 to 5 hours after achievement of hemostasis is reasonable post-ablation.

6.2.2 Antiarrhythmic Drug Therapy

The 2017 Consensus Statement on Catheter and Surgical Ablation for Atrial Fibrillation[7] states that AADs need to be discontinued for at least five half-lives and beta-blockers withheld for at least 24-hours prior to the ablation procedure if a strategy searching for non-pulmonary vein triggers is employed. As

the ablation strategy is left to the discretion of the investigator, other than the requirement for PV isolation, this clinical investigation will not require that all subjects discontinue Class I and III AADs for at least five half-lives. However, AAD usage (start and stop date, time, frequency and dose information) will be documented for the trial prior to and after the subject's procedure(s).

During the blanking period after the ablation procedure, it is recommended that any current AAD medication be continued following the ablation procedure to aid with healing. Current AADs should be withdrawn 4-6 weeks after ablation, unless clinically contraindicated, to assess for recurrence of symptoms and for determination of the need for a repeat ablation during the blanking or therapy consolidation periods. It is recommended that sites phone subjects 4-6 weeks after ablation to remind them to discontinue their AAD medication.

It is recommended that subjects be taken off all Class I and III AADs prescribed for AF/AFL/AT after the blanking and therapy consolidation periods. If the investigator feels that the subject may benefit from a Class I or III AAD during the 9-month evaluation period (post-blanking and therapy consolidation periods), then the investigator should first prescribe a previously ineffective Class I or III AAD up to the historic maximum ineffective dose prior to the ablation procedure. If the historic maximum ineffective dose remains ineffective then a new Class I or III AAD may be initiated.

6.2.3 Vascular Access

It is strongly recommended that vascular access be obtained using ultrasound to minimize complications.

6.2.4 Esophageal Temperature Monitoring

It is strongly recommended that esophageal temperature be monitored using an esophageal temperature probe at the anatomical location nearest the site of energy delivery. Alternatively, esophageal deviation may be performed when ablating near the esophagus.

Termination of energy is strongly recommended if a >1°C rise in esophageal temperature is observed.

6.2.5 Pregnancy Testing

A urine pregnancy test must be performed for women of child-bearing potential, preferably on the day of the procedure.

6.2.6 Thrombus Assessment

Left atrial thrombus assessment by transesophageal echocardiography (TEE) or phased-array intracardiac echocardiography (ICE) must be performed within one day of the ablation procedure or on the day of the procedure.

If a thrombus is discovered within a day of the procedure, the procedure should be postponed, and the subject placed on anticoagulation until the thrombus is resolved and confirmed by imaging. Once confirmation is obtained demonstrating resolution of the thrombus, the inclusion/exclusion criteria should be re-reviewed for the subject to confirm continued eligibility for the trial.

The subject will not need to be re-consented for the trial after the thrombus resolves, provided that the subject meets all eligibility criteria and will undergo an ablation procedure within 90-days of the original consent date unless otherwise indicated by the governing IRB/EC.

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6.3 Initial Ablation Procedure

6.3.1 Ablation Procedure

For those subjects meeting eligibility criteria and who are enrolled in the trial, it is preferable that the ablation procedure be performed within 14-days of consent. Any subject who does not meet eligibility requirements will be a screen failure and will be excluded from this trial.

The subject's rhythm when they enter the EP lab will be documented for the trial. All cardioversions that occur from the time the subject enters the lab to the start of the procedure and during the procedure will be documented.

It is recommended that heparin be administered prior to trans-septal puncture during the AF catheter ablation procedure and adjusted to achieve and maintain an ACT of at least 300 seconds. Use of an ICE probe during the procedure to guide septal puncture and to monitor catheter position and manipulation is strongly recommended. Administration of protamine to reverse heparin is acceptable.

Following trans-septal access, a standard treatment scheme for mapping and ablation should be conducted. Use of robotic systems or Stereotaxis to assist with the procedure is not allowed. Physicians performing ablations must be qualified operators and trained on the study. Each physician who ablates during a particular case needs to be documented on the Procedure CRF.

The procedure should be performed according to the TactiCath SE *Instructions for Use* document using the recommended ablation parameters as noted in the document:

- Power (10 - 30W)
- Contact force (target 20 g, 10-30 g)
- Temperature (37 – 50 °C)
- Irrigation flow rate (17 - 30 ml/min)

When ablating near the left atrial posterior wall, it is recommended that a minimum targeted contact force of 5-10 grams be used as specified in the 2017 HRS Consensus Statement.[7] Recommended maximum parameters for ablating the left atrial posterior wall near the esophagus are:

- Contact force: ≤15 g for ≤10 seconds
- Power: up to 40W

The ablation strategy outlined in **Figure 5** is recommended for initial ablation of all subjects:

1. Perform wide area circumferential ablation to electrically isolate the pulmonary veins.
2. Administer isoproterenol following initial pulmonary vein isolation if the subject is in sinus rhythm to identify gaps in ablation and to identify and ablate any additional AF triggers.
3. Cardiovert the subject before isoproterenol challenge if he/she is not in sinus rhythm after initial pulmonary vein isolation.
4. Ablation of additional cardiac substrate (e.g. ablation of complex fractionated atrial electrograms (CFAE) or linear ablations) should only be considered if sinus rhythm is not restored after isolation of the pulmonary veins and ablation of non-PV triggers.

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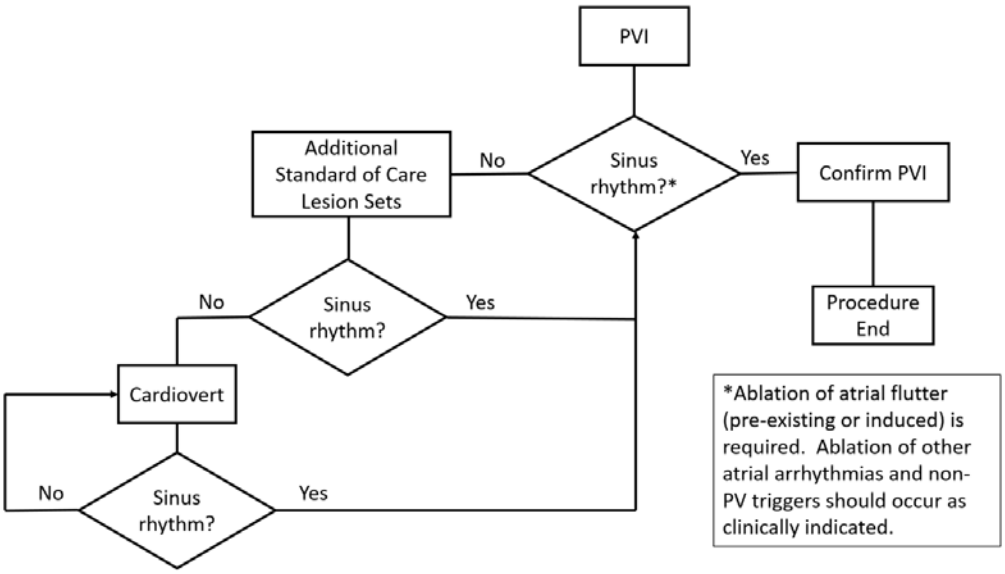
Figure 5. Persistent Atrial Fibrillation Ablation Strategy



All subjects will receive ablations to achieve electrical isolation of the PVs. A minimum 20-minute wait period following electrical isolation of all PVs with assessment and documentation of entrance block is recommended per the 2017 Consensus Statement.[7] It is also recommended in the 2017 Consensus Statement that exit block also be demonstrated.

If PV reconnection occurs during or after the wait period following initial PV isolation of all veins, the vein(s) that reconnected and whether it was successfully isolated after administration of additional ablation lesions will be documented on the CRF. Another wait period is not required after performing touch-up ablation lesions for reconnected PVs.

Subjects with a history of AFL, AT or other SVT (spontaneous or induced) or if these arrhythmias are induced at the time of AF ablation, should undergo additional targeted ablation as clinically indicated. All subjects with a history of typical atrial flutter or induced cavotricuspid isthmus (CTI)-dependent atrial flutter need to undergo concomitant AFL ablation and are recommended to have bi-directional block verified by mapping and pacing maneuvers after initial bi-directional block is achieved.

Additional non-PV AF ablation targets (e.g. linear ablation, elimination of CFAEs, rotational activity, autonomic ganglia, isolation of the left atrial appendage, ablation of scar identified by voltage mapping or MRI, and non-PV triggers) are permitted per the investigator's discretion and will be documented for the trial if sinus rhythm is not restored after isolation of the PVs and ablation of non-PV triggers. If a linear ablation strategy is used, documentation of bidirectional block across the ablation line should be demonstrated and assessed in sinus rhythm and with differential pacing maneuvers. High-dose isoproterenol may be administered to screen for and ablate non-PV triggers. If CFAEs, rotational activity, or non-PV triggers are ablated, the acute goal is elimination of CFAEs, rotational activity, and non-PV triggers and AF termination.

The goal is that the subject is in sinus rhythm at the end of the procedure. If AF cannot be terminated by ablation at the conclusion of the procedure, it is recommended that the patient be cardioverted and PV isolation rechecked.

It is required to verify that the subject has not experienced pericardial effusion at the end of the procedure.

If for any reason, the subject has the TactiCath SE inserted into their vasculature, but no ablation is performed and the subject will not be rescheduled to receive another ablation procedure, the subject will be followed for 30-days to assess safety and then exited from the trial. Follow-up at 30-days will be conducted via a phone call to the subject (may also be an on-site visit). Subjects who will have their ablation procedure re-scheduled will not need to be re-consented for the trial provided they are rescreened (all eligibility criteria met prior to the procedure) within 90-days of the initial consent date.

6.4 Repeat Ablation Procedures

One ablation procedure for treatment of AF/AT/atypical AFL recurrence is allowed during the blanking and therapy consolidation periods (within 180 days post-initial procedure) using the recommended parameters listed in the TactiCath SE *Instructions for Use* document. Note that recurrence and ablation of typical AFL alone does not count as a repeat procedure for AF recurrence.

Certain assessments need to be performed if a repeat ablation is required. Thrombus assessment must be performed prior to ablating the subject. Verification of the exclusion of pericardial effusion must also be performed prior to the conclusion of the procedure.

A 7-day (± 2 days) follow-up phone call or in-person visit to the subject will be conducted after the repeat procedure. All other follow-up visits will occur as previously scheduled from the initial ablation procedure. Note that the 90-day blanking period followed by a 90-day therapy consolidation period are still in place from the initial procedure.

6.5 Pre-Discharge Visit (In-hospital)

Same day discharge after the ablation procedure is not recommended for the study, even if it is considered standard of care at some institutions. Active surveillance of the subject's postoperative care and condition is recommended for at least 72-hours or prior to discharge, whichever occurs first.

<u>The following are required testing for the Pre-Discharge Visit:</u>

- Complete physical exam and 12-lead ECG
- Neurological assessment as recommended in the 2017 Consensus Statement[7]
- Document AAD and anticoagulant drug usage
- Document adverse events and protocol deviations

If the subject requires an extended hospitalization due to a complication or other reason, all pre-discharge testing should be performed prior to discharge, but no later than 72 hours post-procedure.

6.6 Blanking and Therapy Consolidation Periods

A blanking period of 90-days will be employed after the initial ablation procedure, followed by a 90-day therapy consolidation period and then a 9-month evaluation period for a total of 15-months of follow-up.

Early recurrence of AF, AFL, or AT within the blanking period or therapy consolidation period will not be considered treatment failures. During the blanking and therapy consolidation periods, adjustment of antiarrhythmic medications, cardioversions, and one repeat ablation procedure may be performed.

6.7 Follow-up Assessments

Subjects will undergo the following assessments described below at 7-14 days and at 3, 6, 12 and 15-months post-ablation.

7-14 Day Follow-up Visit

This visit constitutes a phone call to the subject after each ablation procedure (initial and if applicable, a repeat procedure). This visit may also be conducted in-person at the site. Documentation for the trial consists of the following:

- Document AAD and anticoagulant drug usage
- Document adverse events and protocol deviations

3-Month (91 + 21 days) Follow-Up Visit

The 3-month follow-up visit is a scheduled in-person site visit. When subjects are seen at the 3-month visit, it is recommended that they are weaned off AADs during the therapy consolidation period if they are doing well and have not discontinued these medications prior to this visit.

- Perform 12-lead ECG
- Document AAD and anticoagulant usage
- Administer the EQ-5D-5L questionnaire as defined in **Section 6.7.2**
- Document adverse events and protocol deviations
- It is recommended to provide the subject with an event monitor for recording at regular intervals (e.g. monthly) and/or for symptomatic events through the 15-month visit.
- It is recommended that a 24-hour Holter be performed
- After the 3-month visit through the end of the study, any signs or symptoms of AF/AFL/AT recurrence should be recorded, and the subject should have either a 12-lead ECG or other form of ECG monitoring per the site's standard practice to determine if recurrence has occurred.

6-Month (181 + 30 days) Follow-Up Visit

The 6-month follow-up visit is an in-person site visit.

- Perform 12-lead ECG
- Document AAD and anticoagulant usage
- Administer the EQ-5D-5L questionnaire as defined in **Section 6.7.2**
- Document adverse events and protocol deviations
- If there are symptoms of AF/AFL/AT present, the subject should have either a 12-lead ECG or other form of ECG monitoring to document the AF/AFL/AT recurrence

- Administer a 24-hour Holter monitor provided by the core laboratory (required)Document any recurrences including details of any repeat electrophysiology studies

12-Month (365 ± 30 days) Follow-Up Visit

The 12-month follow-up visit is an in-person site visit.

- Perform 12-lead ECG
- Document AAD and anticoagulant usage
- Administer the EQ-5D-5L questionnaire as defined in **Section 6.7.2**
- Document adverse events and protocol deviations
- If there are symptoms of AF/AFL/AT present, the subject should have either a 12-lead ECG or other form of ECG monitoring to document the AF/AFL/AT recurrence
- It is recommended that a 24-hour Holter be performed
- Document any recurrences including details of any repeat electrophysiology studies

15-Month (450 ± 30 days) Follow-Up Visit

The 15-month follow-up visit is a scheduled in-person site visit.

- Perform 12-lead ECG
- Document AAD and anticoagulant usage
- Administer the EQ-5D-5L questionnaire as defined in **Section 6.7.2**
- Document adverse events and protocol deviations
- If there are symptoms of AF/AFL/AT present, the subject should have either a 12-lead ECG or other form of ECG monitoring to document the AF/AFL/AT recurrence
- Document any recurrences including details of any repeat electrophysiology studies
- Administer a 24-hour Holter monitor provided by the core laboratory (required)

6.7.1 Unscheduled Visits

If a subject is seen by any physician for possible AF recurrence and/or arrhythmia associated symptoms outside of a regularly scheduled study visit and/or had an urgent care or emergency room visit regarding possible arrhythmia recurrence, these visits need to be documented as “Unscheduled Visits”, unless the visit is already documented on an Adverse Event CRF. If there is an Adverse Event associated with this visit, then an Unscheduled Visit CRF does not need to be completed.

Minimally, the following information should be documented for an unscheduled visit.

- 12-lead ECG, if performed during the visit
- Document AAD and anticoagulant usage
- Document adverse events and protocol deviations

6.7.2 Patient Reported Outcome Measures – EQ-5D-5L Questionnaires

The coordinator or designee will administer patient-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The EuroQol Five Dimensions Questionnaire (EQ-5D-5L) patient-reported outcome measure will be collected for this trial. The EQ-5D-5L questionnaire is a standardized measure of health status that is applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health as well as in population health surveys. EQ-5D-5L is designed for self-completion and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews and takes only a few minutes to complete. The questionnaire includes five dimensions assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is measured based on responses to 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Respondents evaluate their overall health status using a visual analogue scale, which can easily be converted to quality-adjusted life years for cost utility analysis.

Note that it will not be a deviation for the EQ-5D-5L questionnaire be administered by phone. Research personnel should use the EQ-5D-5L Script for Telephone Interview questionnaire for visits conducted over the phone.

6.7.3 Schedule of Events

The schedule of activities specific to this clinical investigation are described in the preceding sections and are summarized in **Table 2**.

Table 2. Schedule of PerAF APAC Clinical Investigation Activities

Activity	**Enrollment / Baseline**	**Procedure** (~14-days of consent)	**Pre-Discharge** (<72 hrs post-proc.)	**7-14 Day Phone Call or In-Person** (7-14 days)	**3-Month In-Person** (91+21 days)	**6-Month In-Person** (181+30 days)	**12-Month In-Person** (365±30 days)	**15-Month In-Person** (450±30 days)
Informed Consent	X							
Demographics	X							
Medical History	X							
Cardiovascular History	X							
AAD & Anticoagulant Medications	X		X	X	X	X	X	X
Physical Examination	X		X					
Neurological Exam	X[1]		X[1]					
NYHA	X							
CHA_2DS_2VASc score	X							
12-Lead ECG	X[2]		X		X	X	X	X
EQ-5D-5L Questionnaire	X				X	X	X	X
24-Hour Holter	X[2]				X[5]	X[5]	X[5]	X[5]
Urine Pregnancy Test		(X)						
Confirm absence of thrombus		X[3]						

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Activity	Enrollment / Baseline	Procedure (~14-days of consent)	Pre-Discharge (<72 hrs post-proc.)	7-14 Day Phone Call or In-Person (7-14 days)	3-Month In-Person (91+21 days)	6-Month In-Person (181+30 days)	12-Month In-Person (365±30 days)	15-Month In-Person (450±30 days)
Ablation procedure		X						
Assess for Pericardial Effusion		X[4]						
Monthly Event Recording					X[6]	X[6]	X[6]	X[6]
Adverse Event Assessment	X	X	X	X	X	X	X	X
Document Deviations	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Withdrawal	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

(X) If applicable

1. A neurological assessment is recommended to be performed as outlined in the 2017 Consensus Statement.
2. Either a 24-hr Holter or 2 ECGs obtained ≥7 days apart may be used to demonstrate continuous AF at Baseline.
3. Thrombus assessment must be performed the day prior to or on the day of the procedure. If a thrombus is discovered, the procedure should be postponed and the subject placed on anticoagulation until the thrombus is resolved as confirmed by imaging.
4. Imaging must be performed prior to the conclusion of the procedure to exclude pericardial effusion.
5. 24-hour Holters must be obtained at the 6-month and 15-month follow-up visits. It is recommended that a 24-hour Holter be obtained at the 3-month and 12-month follow-up visits.
6. It is recommended that event recordings are collected monthly after the initial ablation procedure and whenever the subject is experiencing a symptomatic episode starting at 3-months to 15-months post-procedure as noted in the 2017 Consensus Statement.

6.8 Core Laboratory

A core lab will be used for the collection, interpretation, and collation of data obtained from the following sources:

- 24-hour Holter monitoring at the 6-month and 15-month follow-up visits

The core lab will provide independent review of this data by appropriately trained personnel using standardized procedures to interpret Holter tracings for adjudication of atrial arrhythmias. Findings will be communicated to the investigator and to the Sponsor. The core lab's adjudication findings will be used for analysis.

7.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

Determination of whether there is a reasonable possibility that the device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

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7.1 Adverse Event Definitions and Reporting

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation. This definition includes events related to the medical device under investigation and includes events related to the procedures involved.

7.1.1.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation (after consent is obtained and all eligibility criteria are met). Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. All adverse event data, including deaths, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

For the purposes of this study, the following adverse events will be reported:

- Adverse events that are assessed by the investigator as being related to either the ablation catheter or the ablation procedure will be reported in the database, preferably within 7-days of the site learning of the event
- Serious adverse events, regardless of relatedness to the procedure and/or the ablation catheter will be reported as described in **Section 7.1.2.1**.

Recurrence of AF, AFL, or AT are not considered reportable adverse events unless they occur in severity, frequency, or other manner that is significantly worse than the subject's baseline condition. Recurrence of AF, AFL, or AT will affect the primary effectiveness endpoint and should be reported on the Follow-Up Visit CRF.

Additionally, urinary tract infections (UTIs) that occur after a procedure and do not require a Foley catheter will not be considered adverse events. UTIs that require a Foley catheter will be reported as AEs if related to the procedure or meet serious criteria.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

All adverse events will be collected on each subject through the 15-month follow-up visit.

7.1.2 Serious Adverse Event (SAE) Reporting to Sponsor and IRB/EC

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

   1. a life-threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function, or
   3. in-patient hospitalization or prolongation of existing hospitalization, or

4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

Study site representative will report all SAEs on a Case Report Form (CRF) in the database . When the system is down for more than 24 hours, sites will be directed to utilize the Clinical Adverse Event case report form (CRF) for Adverse Event (AE) and send to the Sponsor via email at [redacted]

7.1.2.1 SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor **no later than 3 calendar days from the day the site personnel became aware of the event** or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.1.3 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

7.1.4 Independent Adjudication of Adverse Events

Independent review and adjudication of pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation will be performed by qualified physicians not participating in the PerAF APAC trial as defined in the charter and according to definitions provided in this CIP, which will be used for assessment of the safety secondary endpoint.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation.

[redacted]

8.2 Statistical Analyses

The primary endpoints and additional evaluation analyses will be summarized descriptively based on available data or measurements in the analysis population. No formal hypothesis testing will be performed.

8.2.1 Primary Safety Endpoint Analysis

The primary safety endpoint will be summarized as the percentage of subjects who experienced one or more primary safety endpoints. The primary safety analysis population for the primary safety endpoint will be subjects in the primary analysis population who have completed their 7-day follow-up visit; or crossed the end of the 7-day visit window without the visit but with a primary safety endpoint event. Subjects without an event that are lost to follow up without a visit at or beyond their 7-day follow up visit window will be excluded from this analysis.

The primary safety endpoint event rate will be calculated based on the number of subjects experiencing a primary safety endpoint event divided by the total number of subjects in the analysis population. Relatedness of the event to the catheter and to the procedure will be determined by the independent physician reviewer.

8.2.2 Additional Data Analyses

Additional data to be collected in this clinical investigation are described and will be reported using summary statistics. No hypothesis tests will be performed.

In general, continuous (CONT) variables will be summarized with the numbers of observations, means with standard deviations, quartiles, minimums, maximums as per the table mockups.

Categorical (CAT) variables will be summarized with subject counts and percentages/rates, and where specified in the table mockups.

Survival (SURV) analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Subjects withdrawn or otherwise lost to follow-up during the follow-up period will be censored at their last known visit. Survival data will be presented using the Kaplan-Meier product limit method.

The following list of analyses describes how the additional evaluations will be analyzed:

- Acute procedural success, defined as confirmation of entrance block in all pulmonary veins (CAT)
- Proportion of subjects off all Class I or III AADs taken to treat AF/AFL/AT at 15-months (SURV)
- Proportion of subjects who achieve 15-month single procedure success, defined as freedom from documented AF/AFL/AT recurrence (episodes >30 seconds) during the 9-month period following the blanking and therapy consolidation periods after a single ablation procedure (SURV)
-
- Changes in EQ-5D-5L scores from baseline to follow-up at 3, 6, 12, and 15-months after the initial procedure (CONT)

8.4 Timing of Analysis

Data analyses will be performed at the completion of the 15-month follow-up period for all subjects or as desired by the Sponsor. In addition, study progress and data may be summarized and reported as needed.

8.5 Subgroup Analysis

No subgroup analyses are planned for this clinical investigation.

8.6 Multiplicity

No hypothesis testing will be performed; therefore, no adjustments will be made for multiplicity in the endpoint analyses.

8.7 Procedures for Accounting for Missing Data

Every effort will be made to collect all required data. All data available for the endpoints specified among the analysis population will be used. Missing data will not be imputed. Kaplan-Meier analysis will censor subjects withdrawn or otherwise lost-to-follow-up at last known visit.

8.8 Planned Interim Analysis

No interim analyses are planned for this study.

8.9 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.10 Success Criteria

Pass/Fail criteria do not apply to this study.

8.11 Deviations from Statistical Plan

Any major changes or less significant changes to the planned statistical analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

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Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB/EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.3 Training

10.3.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.3.2 Training Required for the Use of the Device

All investigators involved in the conduct of this clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately. Each ablating physician must have contact force sensing experience and must have experience using EnSite Precision for AF treatment prior to site activation.

10.4 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Clinical Trial Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.5 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures,

including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

10.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.7 Committees

10.7.1 Steering Committee

The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review operational issues that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

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11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)

- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results. It is acceptable to have labs and/or ECGs reviewed and annotated in the electronic medical record system for site's that have these capabilities. For those sites that do not have such capability, the labs and ECGs should be printed and signed by the investigator.
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

11.4 Case Report Form Completion

Worksheets will be provided to sites under separate cover for review of the required data collection for the trial. Sites may also create their own worksheets for data collection.

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports. Data will be collected on CRFs for all subjects that are enrolled in the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The clinical investigation report will be provided to investigators within one year of the end of the investigation and the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

The Sponsor will be responsible for determining whether to register the clinical investigation on www.clinicaltrials.gov or any other clinical trials, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the clinical investigation should be registered, Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation.

15.0 RISK ANALYSIS

Risks associated with the device are managed in accordance with ISO 14971. The risk analysis included an objective review of published and available unpublished medical and scientific data. The sections below provide an overview of residual risks identified in the risk management report and anticipated benefits of the medical device. The additional tests and assessments required by the clinical investigation were analyzed for additional risks and are incorporated in the sections below.

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15.1 Anticipated Clinical Benefits

While there is no guaranteed clinical benefit associated with participation in this study, it is expected that TactiCath SE will have similar benefits as other commercially available ablation catheters in maintaining sinus rhythm. The clinical benefits of sinus rhythm are well established and include relief of symptoms and improvements in exercise tolerance, hemodynamics, LV function, and quality of life. Restoration of sinus rhythm may confer a mortality benefit.

The information gathered from this study will also add to the understanding of the treatment options for subjects with persistent AF. This knowledge may advance medical science and have a benefit on other subjects with a similar arrhythmia.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and procedure are listed below. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

The following is a list of anticipated adverse device effects:

- Air embolism
- Anesthesia reaction
- Aorto-right atrial fistula
- Arrhythmias, bradycardia, and tachycardia
- Arteriovenous fistula
- Cardiac perforation/tamponade
- Cardiac thromboembolism
- Cerebrovascular incident or Attack / Stroke
- Chest pain/discomfort
- Coronary artery dissection
- Coronary artery spasm
- Coronary artery thrombosis / occlusion
- Death
- Diaphragmatic paralysis
- Dislodgement of implantable cardioverter defibrillator or permanent pacing leads
- Endocarditis
- Gastroparesis
- Heart failure / pump failure
- Hemothorax
- Hospitalization (initial and prolonged)
- Increased creatinine phosphokinase (CPK) level
- Infections
- Laceration
- Leakage of air or blood into the lungs or other organs due to perforation
- Left atrial-esophageal fistula
- Major bleeding, requiring surgery or transfusion
- Myocardial infarction
- Obstruction or perforation or damage to the vascular system

- Pericarditis
- Pericardial effusion
- Phrenic nerve damage including diaphragmatic paralysis
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Pulmonary vein dissection
- Pulmonary vein thrombus
- Pulmonary hypertension
- Respiratory depression
- Skin burns
- Severe PV stenosis (>70%), or complete occlusion of a PV, even in the absence of symptoms
- Tamponade, potentially requiring surgery
- Temperature elevation or fever
- Transient ischemic attack (TIA)
- Thromboembolism
- Thrombosis
- Unintended complete or incomplete AV, sinus node, or other heart block or damage
- Valvular damage
- Vascular bleeding/local hematomas/ecchymosis
- Vasovagal reactions
- Ventricular tachyarrhythmia
- Volume overload

15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Analysis Report

The risk analysis for TactiCath SE was performed based on in-house tools to systematically identify potential hazards associated with the design and use of the device. Based upon the preclinical, clinical (Earliest generation of catheter – TOCCATA trial (NCT01223469), EFFICAS I and II trials (NCT02131337), TOCCASTAR trial (NCT01278953), Next generation of catheter - TOCCASTAR Supplemental Clinical Study (NCT01278953), and TactiCath Quartz Post Approval Study (NCT02310100)) and bench-testing data, all risks have been identified and determined to be within acceptable levels.

No additional residual risk has been identified with the use of the TactiCath SE catheter.

15.4 Risks Associated with Participation in this Clinical Investigation

Possible risks associated with participating in this clinical study are not anticipated to be any different from risks associated with undergoing procedures with commercially available TactiCath SE. Protocol required assessments are summarized in **Section 6.7.3**. These assessments are standard of care for TactiCath SE and as such do not pose any additional risks.

15.5 Possible Interactions with Protocol-Required Concomitant Medications

There are no known interactions with protocol-required concomitant medications.

15.6 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding patient selection, device handling, and device placement are included in the IFU. It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the device including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, and study monitoring to ensure adherence to the protocol. All adverse events will be reported to the Sponsor as summarized in **Sections 7.1.1.1 - 7.1.1.4** and will be monitored internally for safety surveillance purposes.

Device Design: The catheter has a contact force magnetic sensor which plays an important factor in achieving transmural lesions that is critical in abolishing the substrate necessary for an arrhythmia and AF in particular. With increasing force, a greater proportion of the electrode surface area is in contact with the tissue, and there is more efficient energy coupling. Gaps in ablation lines are commonly seen when the amount of contact force over the RF delivery time is low and this is associated with higher recurrence rates after ablation for AF. Contact force-sensing ablation catheters such as TactiCath SE provide a valuable feedback mechanism to help ensure the efficacy of ablation.

Investigator Selection and Training: Investigators will be selected as outlined in **Section 10.1**. Sites will receive training as stated in **Section 10.3.1**. Additionally, ablating physicians will be qualified and have experience using a contact force sensor as stated in **Section 10.3.2**.

Adherence to the Clinical Investigational Protocol: The clinical study will be monitored by the Sponsor to ensure adherence to the CIP. Subjects will be carefully selected through rigorous screening using pre-specified inclusion and exclusion criteria as stated in **Section 5.3.** Adverse events will be reported to the Sponsor and will be monitored internally for safety surveillance purposes and reported to regulatory authorities as applicable. Adverse events will be adjudicated by qualified physicians who are not participating in the study.

15.7 Risk to Benefit Rationale

An extensive risk analysis and risk mitigation plan (as summarized in **Section 15.3**) has been implemented to minimize any residual risk of the TactiCath SE to the subject. Treatment with TaciCath SE has all the benefits of a state-of-the-art cardiac ablation therapy with the added benefit being able to monitor contact force at the catheter tip. The residual risks are outweighed by the benefits, as described in the previous sections, and the overall risk has been determined to be acceptable.

16.0 REFERENCES

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APPENDIX II. ABBREVIATIONS AND ACRONYMS

All relevant abbreviations and acronyms specific to this clinical investigation are outlined in the table below.

Acronym/Abbreviation	Description
AAD	Antiarrhythmic drug
AE	Adverse event
AF	Atrial fibrillation
AFL	Atrial flutter
APHRS	Asia Pacific Heart Rhythm Society
AT	Atrial tachycardia
CFAE	Complex fractionated atrial electrograms
CIP	Clinical investigation plan
CRF	Case report form
CRT-D	Cardiac resynchronization therapy defibrillator
CTI	Cavotricuspid isthmus
CVA	Cerebrovascular accident
DMP	Data Management Plan
EC	Ethics Committee
ECAS	European Cardiac Arrhythmia Society
ECG	Electrocardiogram
EDC	Electronic data capture
EHRA	European Heart Rhythm Association
EQ	EuroQol Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRS	Heart Rhythm Society
ICE	Intracardiac echocardiography
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent form
IDE	Investigational device exemption
IFU	Instructions for Use
INR	International normalized ratio
IRB	Institutional Review Board
LAD	Left atrial diameter
LCD	Liquid crystal display
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NIHSS	National Institutes of Health Stroke Scale
NOAC	Novel oral anticoagulant
NYHA	New York Heart Association
OPC	Objective performance criterion
PCI	Percutaneous coronary intervention
PMA	Pre-market approval
PTE	Per treatment evaluable

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Acronym/Abbreviation	Description
PV	Pulmonary vein
RF	Radiofrequency
SAE	Serious adverse event
SE	Sensor enabled
SOLAECE	Latin America Society of Electrophysiology and Cardiac Stimulation
SVT	Supraventricular tachycardia
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TTE	Transthoracic echocardiogram
TTM	Transtelephonic monitoring
UADE	Unanticipated adverse device effect
UTI	Urinary tract infection

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APPENDIX III. DEFINITIONS

The following definitions will be used by the independent, qualified physicians that will determine whether the events listed below constitute a device or procedure related serious adverse event included in the primary endpoint. Most of the definitions have been adapted from the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus on AF Ablation.[7]

Primary Safety Event	Description
Atrioesophageal fistula	A connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium, such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrioesophageal fistula.
Bleeding	Bleeding is a major complication of AF ablation if it requires and/or is treated with transfusion or results in a 20% or greater fall in hematocrit.
Cardiac tamponade/perforation	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade/perforation should also be classified as "early" or "late" depending on whether it is diagnosed during or following initial discharge from the hospital.
Death	Adverse event resulting in the patient's death.
Heart block (AV block)	New, persistent 2nd or 3rd degree AV block not attributable to a vasovagal reaction or medication effect and requiring permanent pacing.
Myocardial infarction	Irreversible necrosis of heart muscle secondary to prolonged ischemia with at least one of the following three criteria: (2) Detection of ECG changes indicative of new ischemia (new ST-T wave changes or new LBBB) that persist for more than 1 hour; (3) Development of new pathological Q waves on an ECG; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Pericarditis	Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Phrenic nerve injury resulting in diaphragmatic paralysis	Phrenic nerve paralysis is defined as absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pneumothorax	Abnormal collection of air in the pleural space between the lung and the chest wall that prolongs the hospital stay (for observation) or requires surgical intervention or chest tube placement.
Pulmonary edema	Excess fluid in the lungs that includes all of the following: • Symptoms (e.g. dyspnea) • Physical findings (e.g. rales, hypoxemia) • Radiologic findings • Response to diuretic therapy • Requires hospitalization
Pulmonary vein stenosis	Reduction of the diameter of a pulmonary vein or a pulmonary vein branch of ≥70% confirmed via imaging (CT or MRI).
Stroke / cerebrovascular accident	Stroke diagnostic criteria:

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Primary Safety Event	Description
	• Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. • No other readily identifiable nonstroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). • Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MRI or CT scan or cerebral angiography); lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)
Thromboembolism	An arterial or venous thrombus that results in deep vein thrombosis, pulmonary embolism, or peripheral arterial embolism.
Transient ischemic attack	New focal neurological deficit of vascular (occlusive) origin with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours determined by the consulting neurologist; neuroimaging without tissue injury.
Vascular access complication	Vascular access complications include development of a hematoma, an AV fistula, or a pseudoaneurysm. A major vascular complication is defined as one that requires intervention, such as surgical repair or transition, prolongs the hospital stay, or requires hospital admission.

Clinical Investigation Plan

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Clinical Investigation Plan

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Clinical Investigation Plan

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