ABLATE POST APPROVAL STUDY

ATRICURE SYNERGY ABLATION LESIONS FOR NON-PAROXYSMAL FORMS OF ATRIAL FIBRILLATION TREATMENT DURING CONCOMITANT ON-PUMP ENDO/EPICARDIAL CARDIAC SURGERY

Protocol Number: CP2011-1

Sponsor: *AtriCure, Inc.*

[redacted]

[redacted]

PAS Steering Committee [redacted] **Chairperson**

[redacted]

Issue Date/Version: 11 April 2014 / Version L

Amendment Date /Version: 23 June 2014 / Version M

Confidential Material:

Protocol Signature Page

The signature below constitutes the Investigator has reviewed the protocol and the attachments, and agrees to provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH/GCP guidelines.

Investigational Site Name: _____

Investigator Designation (please select as appropriate) :

☐ Principal Investigator ☐ Physician Sub-Investigator ☐ Non-Physician Sub-Investi

Investigator Name (*Print*): _____

Investigator Signature: _____

Date of Signature (*DD-Month-YYYY*): _____

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PROTOCOL SUMMARY

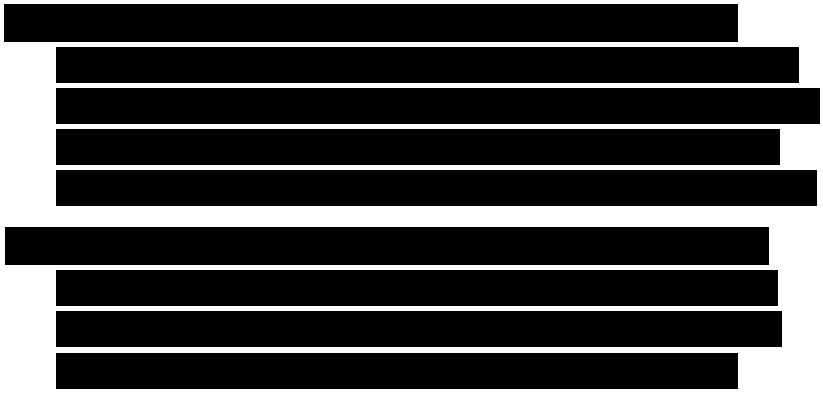
Title:	AtriCure Synergy RF Energy Lesions For Non-Paroxysmal Forms Of Atrial Fibrillation Treatment During Concomitant On-Pump Cardiac Surgery Post-Approval Study (or "ABLATE PAS")
Device:	The AtriCure Synergy Ablation System [redacted] • [redacted]
Objective:	The primary objective of this post-approval study is to evaluate clinical outcomes in a cohort of patients treated during commercial use of the AtriCure Synergy Ablation System by physicians performing the Maze IV procedure.
Design:	This prospective, open label, multi-center, observational, single arm registry is designed to monitor the AtriCure Synergy Ablation System continued safety and efficacy during the peri-procedural and long term phase during commercial use in patients being treated for non-paroxysmal forms of atrial fibrillation (AF) who are undergoing a concomitant open, on-pump cardiac surgical procedure.
Primary Efficacy Outcome:	The proportion of patients free from AF (i.e. no episodes lasting > 30 continuous seconds duration of either Atrial Fibrillation, Atrial Flutter or Atrial Tachycardia) while off Class I and III antiarrhythmic drugs for at least 4 weeks (except amiodarone which must be 12 weeks prior to assessment), as determined by an independent core lab assessment of 48 hour Holter, Zio™ Patch or PPM interrogation recording performed at a minimum of 12, 24 and 36 months postoperatively (hypothesis test at 36 months).
Primary Safety Outcome:	• The proportion of patients with any serious device or ablation procedure-related adverse events [redacted] within 30 days post-procedure or hospital discharge (whichever is later) as adjudicated by a Clinical Events Committee.

Secondary Efficacy Outcome:

- The proportion of patients free from AF, regardless of AAD usage (i.e. no episodes lasting > 30 continuous seconds duration of either Atrial Fibrillation, Atrial Flutter or Atrial Tachycardia), as determined by an independent core lab assessment of 48 hour Holter, Zio™ Patch or PPM interrogation recording performed at a minimum of 12, 24 and 36 months postoperatively.

Secondary Safety Outcomes:

- Composite major adverse event: Serious adverse events occurring post-operatively within 30 days post-procedure or hospital discharge (whichever is later) including:
  - Death (includes deaths after 30 days or hospital discharge if death is procedure related).
  - Stroke (resulting in significant permanent disability)
  - TIA
  - Myocardial infarction, and
  - Excessive bleeding (requiring >2 units of blood replacement and surgical intervention).



- Pacemaker implantation (PPM) within 30 days post procedure will be summarized and reported by reason for PPM (i.e., sinus node dysfunction, AV-node, etc.).

Planned Enrollment: Up to 390 subjects.

Population: Subjects who have non-paroxysmal forms of AF and are scheduled to undergo a primary open cardiac surgical procedure requiring cardiopulmonary bypass including valve surgery and/or CABG.

Follow-up Schedule: All patients will undergo clinical follow-up in hospital and at 30 days, 4, 12, 24 and 36 months post procedure.

Number of Sites: 50 study centers located in North America

Study Duration (Estimated):
Study Start: Q3/2012
Enrollment Completion: Q4/2014
Follow Up Completion: Q4/2017
Final Report: Q2/2018
(See detail in section 6.5)

Inclusion Criteria:

- Age ≥ 18 years.
- Subjects with Persistent or Longstanding Persistent Atrial Fibrillation defined in accordance to HRS AF expert consensus statement (2012) [1]
  - Persistent AF is defined as continuous AF that is sustained beyond seven days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
  - Longstanding persistent AF is defined as continuous AF of greater than 12 months duration.
    - The performance of a successful cardioversion (sinus rhythm >30 seconds) within 12 months of an ablation procedure with documented early recurrence of AF within 30 days should not alter the classification of AF as long-standing persistent
- Subject is scheduled to undergo elective open cardiac surgical procedure(s) to be performed on cardiopulmonary bypass for one or more of the following: Coronary Artery Bypass Grafting (CABG), Mitral valve repair or replacement, Aortic valve repair or replacement, Tricuspid valve repair or replacement. In conjunction with these procedures Patent Foramen Ovale (PFO) or A Septal Defect (ASD) repair are allowed.
- The patient (or their legally authorized representative) agrees to participate in this study by signing the IRB approved informed consent form.
- Willing and able to return for scheduled follow-up visits.

Exclusion Criteria:

- Stand alone AF without indication(s) for concomitant cardiac surgery.
- Need for emergent cardiac surgery (i.e. cardiogenic shock).
- Preoperative need for an intra-aortic balloon pump or intravenous inotropes
- Pregnancy or desire to get pregnant for the duration of the study (concomitant surgical procedure through the thirty six (36) month follow-up period).
- Enrolled in another clinical trial that could confound the results of this study.

Sample Size:

The study will enroll up to 390 subjects at 50 North American sites. [redacted] This number of subjects shall provide an adequate sample to fully assess the outcome of the procedure within a broad population and should supply a sufficient number of subjects for both 30 day safety evaluation [redacted] and long term efficacy evaluation [redacted]

Steering Committee: [redacted]

Sponsor/Manufacturer, Study Coordination and Monitoring:

AtriCure, Inc.

[redacted]

[redacted]

1.0 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Clinical Information

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia seen in clinical practice, particularly in the elderly, and is an important risk factor for stroke. AF accounts for 34% of arrhythmias as the principal diagnosis.[1]

AF is a condition in which there are highly asynchronous atrial depolarization without effective atrial contraction. AF is also characterized by the presence of rapid, irregularly timed impulses reaching the AV node from the atrium and is associated with irregularly timed ventricular response. The atrial rate can be between 350 to 600 beats per minute. Due to the low pass filtering properties of atrio-ventricular (AV) node, the ventricular response is much slower.

It is estimated that 2.2 to 5.1 million people in the U.S. have AF.[2,3] The prevalence of AF increases with age. The condition affects fewer than 1% of people under age 60, with nearly 4% of people 60 years and older and 9% of people 80 years and older having been diagnosed with AF.[4] In 85-95% of cases, the presence of AF is related to the presence of underlying heart disease, left atrial enlargement, or abnormal atrial electrophysiology.

AF can lead to thromboembolism and stroke in approximately 5 -10% of high-risk patients.[5] Risk increases with age and with the coexistence of structural heart disease, such as mitral regurgitation, which is common in these patients. Because there are no effective atrial contractions, areas of blood stasis are set up in the atria (particularly in the appendages) and clot sometimes forms. In about 5% of patients with AF, clotted blood dislodges from the atria and causes stroke. The American Heart Association estimates that in the United States, AF is responsible for over 70,000 strokes each year. In just the United States, it is estimated that AF accounts for 1.4 million outpatient visits and over 227,000 hospitalizations per year.[2,3]

2.0 AtriCure System

The trial is designed as a Post Approval Study to investigate the acute and long-term outcomes of the AtriCure Synergy Ablation System. The product has been used in previously clinical IDE trials (RESTORE and ABLATE) that were used to support market approval of the system. The clinical results were presented to the FDA Advisory Panel in October of 2011. This group recommended approval this product. FDA accepted their recommendation and the Synergy Ablation System received approval in December 2011. A condition of this approval is to conduct this Post Approval Study aimed at collecting information on the acute and longer term outcomes on the product when used to complete the MAZE IV procedure in a commercial setting.

3.0 ATRICURE SYNERGY ABLATION SYSTEM LABELING

3.1 Indications for Use

The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent atrial fibrillation (sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion) or longstanding persistent atrial fibrillation (continuous atrial fibrillation of greater than 12 months duration) in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.

3.2 Contraindications

The AtriCure Synergy Ablation System should not be used for contraceptive coagulation of fallopian tubes. The device is not designed for safe and effective use for that purpose.

3.3 Warnings and Precautions

The warnings and precautions can be found in the AtriCure Synergy Ablation System Instructions for Use.

4.0 ATRIAL FIBRILLATION CLASSIFICATION

In an effort to bring uniformity to the various nomenclature being used in the medical community, the Heart Rhythm Society Task Force on Catheter and Surgical Ablation (HRS/EHRA/ECAS) have recommended the following AF classification scheme based upon the patterns of duration and mode of termination[1].

- Paroxysmal AF is defined as recurrent AF ($\geq$2 episodes) that terminates spontaneously within 7 days. Episode of AF $\leq$48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.

- Persistent AF is defined as continuous AF that is sustained beyond seven days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after $\geq$48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.

- Longstanding persistent AF is defined as continuous AF of greater than 12 months duration. The performance of a successful cardioversion (sinus rhythm >30 seconds) within 12 months of an ablation procedure with documented early recurrence of AF with30 days should not alter the classification of AF as long-standing persistent.

  The ABLATE Post Approval Study (ABLATE PAS) will focus on those patients with non-paroxysmal forms of AF who meet the inclusion/exclusion criteria defined in **Section 9** of this protocol.

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5.0 STUDY OBJECTIVE

The primary objective of this ABLATE Post-Approval Study (or "ABLATE PAS") is to evaluate clinical outcomes in a cohort of patients receiving treatment with the AtriCure Synergy Ablation System in performing the Maze IV procedure. The efficacy of the device will be demonstrated by establishing that the device effectively eliminates non-paroxysmal forms of atrial fibrillation. Elimination of non-paroxysmal forms of atrial fibrillation will be assessed by a 48 hour Holter Monitor, Zio™ Patch, or PPM

interrogation [redacted] after the procedure that demonstrates no signs of atrial fibrillation/atrial flutter/ atrial tachycardia longer than 30 seconds as assessed by an independent core laboratory.

Safety shall be assessed in the study using the incidence of serious device or ablation procedure related adverse events which occur within 30 days post-procedure or hospital discharge (whichever is longer).

6.0 STUDY DESIGN

The ABLATE PAS is a multi-center, prospective, observational study designed to evaluate the AtriCure Synergy Ablation System for continued safety and efficacy during commercial use in a real world settings in patients with non-paroxysmal forms of AF. One of the goals of a post approval study is to assure that the provider and subject population are representative of the general population.

[redacted]

[redacted]

6.2 Study Center Initiation/Start Up

The ABLATE PAS will utilize the existing subjects and sites currently involved in the ABLATE AF Registry. It is anticipated that at the initiation of ABLATE PAS a total of 75 subjects will be enrolled at the 20 ABLATE AF sites. [redacted]

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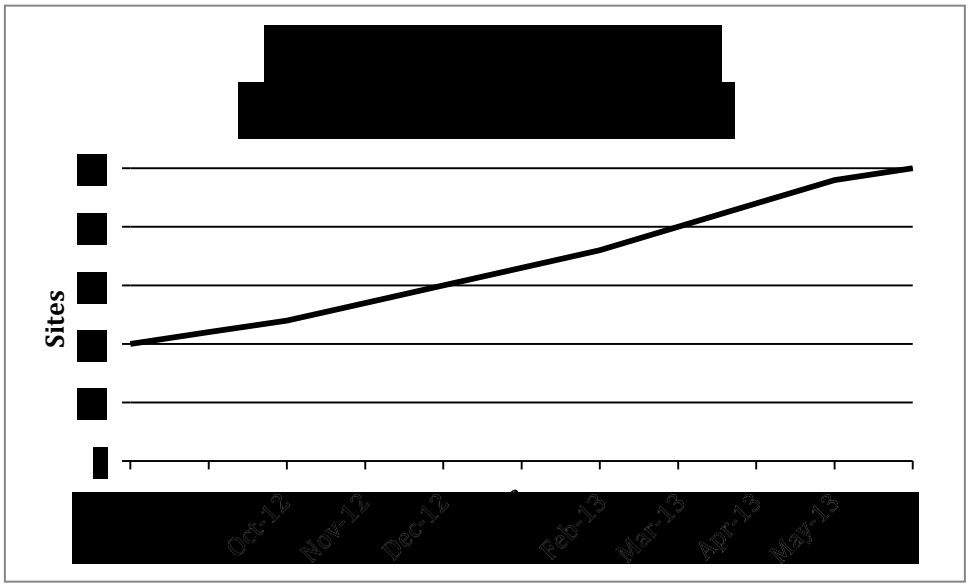
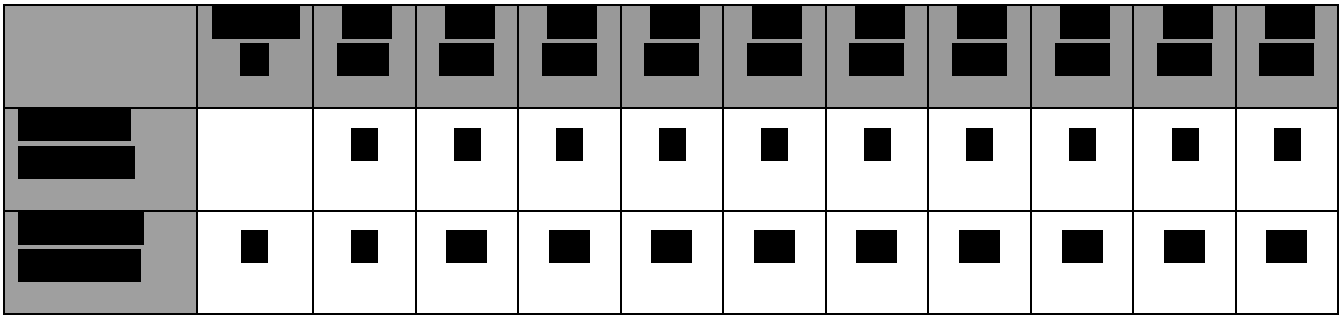


6.3 Enrollment Procedures

All patients presenting with non paroxysmal (AF) and who are scheduled to undergo a primary open cardiac surgical procedure requiring cardiopulmonary bypass including valve surgery and/or CABG are potential study candidates for the ABLATE PAS. Potential patients will be pre-screened to confirm AF classification (persistent or longstanding persistent) for eligibility and offered the chance to participate in the study. Patients will not undergo any protocol specific assessments that are not considered to be standard of care prior to signing the informed consent form for the study. A Patient Screening Log will be provided to the study sites, in order to maintain a cumulative log of all screened patients. The reason for ineligibility will be documented on the study screening log including patients who refuse to participate in the study.

Each investigator will recruit subjects equitably in an effort to ensure to the best extent possible that the subject pool is representative in gender, race, ethnicity, and age of the population affected by the condition being studied.

[redacted]



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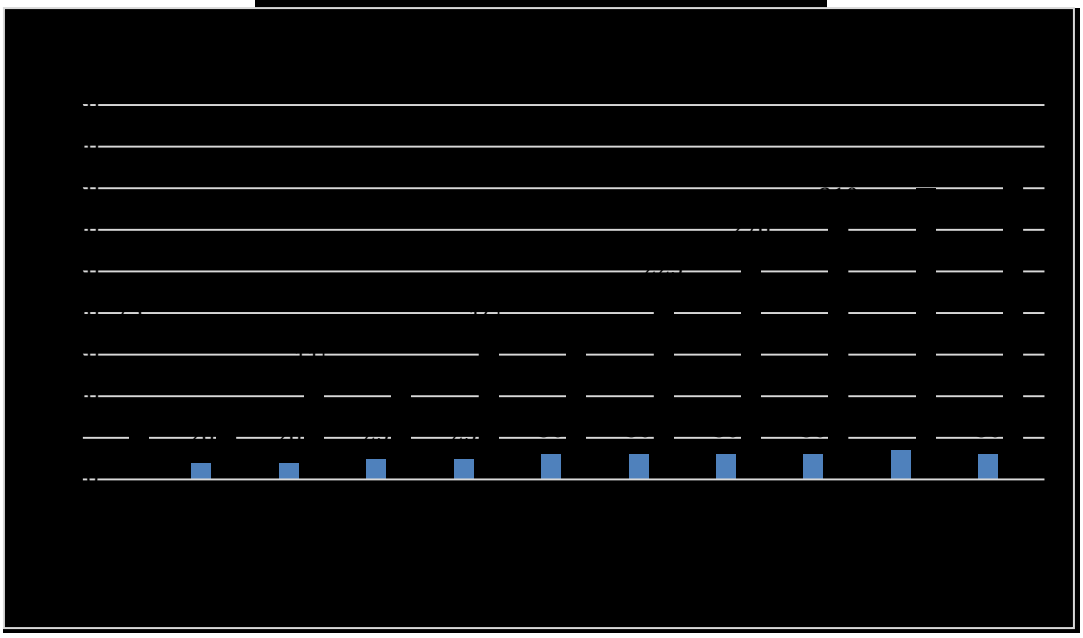
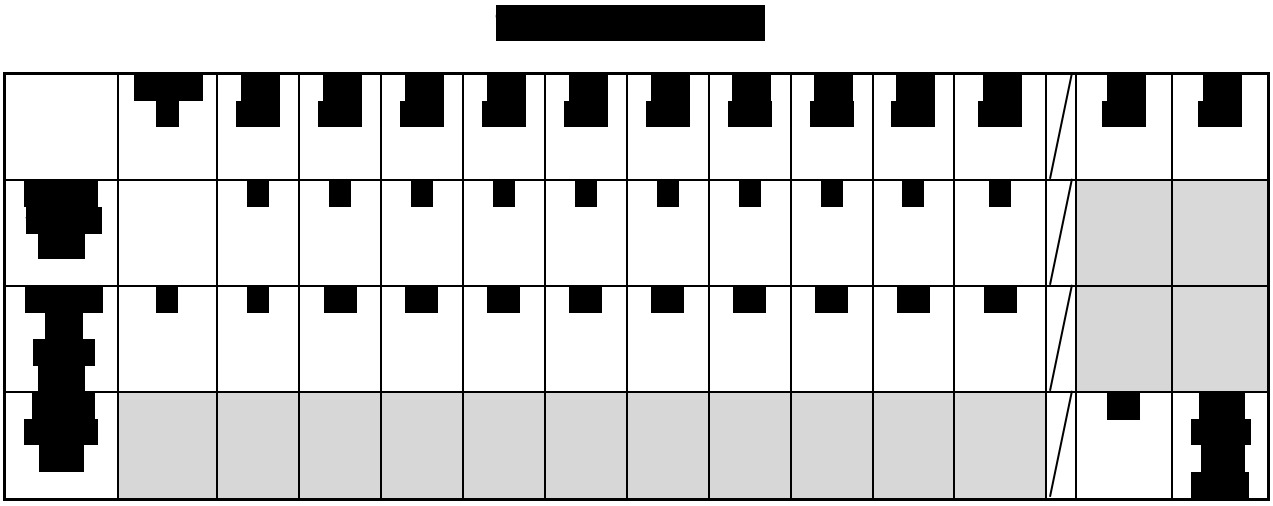


6.4 Informed Consent Procedures

Informed consent must be obtained from a potential patient or their legally authorized representative prior to conducting any preoperative assessments that are not part of the routine preparation and evaluation of a patient for their scheduled open-heart procedure or evaluation of atrial fibrillation, even though the patient's eligibility has not yet been fully established. If during the course of the pre-operative evaluations, a treatment patient is found not to be eligible for inclusion in the study, the patient or their representative should be notified and the reason for ineligibility documented on the screening log.

[redacted]



7.0 STUDY OUTCOMES

The ABLATE PAS will utilize a 48 hour Holter, Zio™ Patch or PPM interrogation performed at follow up [redacted] to assess efficacy (i.e. freedom from AF). Additionally, secondary efficacy outcomes will be reported [redacted] post-operatively. The Holter Monitor, Zio™ Patch or PPM interrogation data shall be reviewed by an independent Core Laboratory [redacted]

The following are the primary and secondary efficacy outcomes for this ABLATE Post-Approval Study:

7.1 Primary Efficacy Outcome

The proportion of patients free from AF (i.e. no episodes lasting > 30 continuous seconds duration of either Atrial Fibrillation, Atrial Flutter or Atrial Tachycardia) while off Class I and III antiarrhythmic drugs for at least 4 weeks (except amiodarone which must be 12 weeks) prior to assessment), as determined by an independent core lab assessment of 48 hour Holter, Zio™ Patch or PPM interrogation recording performed [redacted]

7.2 Secondary Efficacy Outcome

The proportion of patients free from AF, regardless of AAD usage (i.e. no episodes lasting > 30 continuous seconds duration of either Atrial Fibrillation, Atrial Flutter or Atrial Tachycardia), as determined by an independent core lab assessment of 48 hour Holter, Zio™ Patch or PPM interrogation recording performed [redacted]

7.3 Primary Safety Outcome

The proportion of patients with any serious device or ablation procedure-related adverse event within 30 days post-procedure or hospital discharge (whichever is later).

7.4 Secondary Safety Outcomes

In addition to the primary safety outcome discussed above the following safety outcomes will be evaluated:

- Composite major adverse event: Serious adverse events occurring post-operatively within 30 days of procedure or hospital discharge (whichever is later) including:
    - Death (includes deaths after 30 days or hospital discharge if death is procedure related).
    - Stroke (resulting in significant permanent disability)
    - TIA
    - Myocardial infarction, and
    - Excessive bleeding (requiring >2 units of blood replacement and surgical intervention).

All serious adverse events that are reported in the study shall be summarized and reported. The events shall be summarized at each follow up interval based upon level of seriousness (serious vs. non-serious) and attribution (device, ablation procedure, procedure to address structural heart disease, co-morbid condition, etc.) to provide a complete profile of the acute and long-term safety of the device and procedure.

- Device and ablation procedure-related serious adverse events summarized and reported by type of surgical procedure (i.e. surgical procedure to address structural heart disease).
- Permanent Pacemaker Implantation (PPM) occurring within 30 days post procedure will be summarized and reported by reason for PPM implantation (i.e., sinus node dysfunction, AV node, etc.).

8.0 DEVICE DESCRIPTION, POTENTIAL RISK BENEFITS & STUDY JUSTIFICATION

The approved AtriCure Synergy Ablation System devices [redacted]

Refer to the Instructions for Use (IFU) for descriptions, indications for use, contraindications, system preparation, precautions and warnings.

8.1 Potential Risks and Benefits

A summary of the risks and benefits of the AtriCure system are outlined in the product Instructions for Use (IFU) [redacted]

9.0 ELIGIBILITY CRITERIA

9.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years
- History of a non-paroxysmal form of atrial fibrillation as defined by the HRS/EHRA/ECAS Consensus Statement.

  - Persistent AF shall be defined as continuous AF that is sustained beyond seven days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
  - Longstanding persistent AF shall be defined as continuous AF of greater than 12 months duration. The performance of a successful cardioversion (sinus rhythm >30 seconds) within 12 months of an ablation procedure with documented early recurrence of AF with30 days should not alter the classification of AF as long-standing persistent.

    Note: For both types of AF, two (2) electrocardiograms (e.g. 12-lead ECG, Holter, event monitor, Implantable Loop Recorder (ILR), Pacemaker, Zio™ Patch, etc.) documenting AF, with electrocardiograms taken at least 7 days apart, for subjects with sustained AF ≥7 days. Holter, event monitor, ILR, Zio™ Patch or pacemaker recordings need to show continuous AF.

- Subject is scheduled to undergo elective open cardiac surgical procedure(s) to be performed on cardiopulmonary bypass for one or more of the following: Coronary Artery Bypass Grafting, Mitral valve repair or replacement, Aortic valve repair or replacement, Tricuspid valve repair or replacement. In conjunction with these procedures patent foramen ovale (PFO) or atrial septal defect (ASD) repair are allowed.
- The patient (or their legally authorized representative) agrees to participate in this study by signing the IRB approved informed consent form.
- Willing and able to return for scheduled follow-up visits.

9.2 Subject Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Stand alone AF without indication(s) for concomitant cardiac surgery.
- Need for emergent cardiac surgery (i.e. cardiogenic shock).
- Preoperative need for an intra-aortic balloon pump or intravenous inotropes.
- Pregnancy or desire to get pregnant for the duration of the study (concomitant surgical procedure through the thirty six (36) month follow-up period).
- Enrolled in another clinical trial that could confound the results of this study.

10.0 REASONS FOR WITHDRAWAL

A study subject will be discontinued from participation in the study if:

- The investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures would not be in the best interest of the subject.

Non-compliance will be clearly documented in the subject's source documentation (i.e., progress notes, medical records, etc.)

- The subject is lost to follow up. A subject will be considered "lost to follow-up" and terminated from the study when all of the following criteria have been met:
  - Failure to complete the remainder of the scheduled study visits without due cause; and
  - Documentation of three unsuccessful attempts to contact the subject via telephone and by certified mail.
- The subject wishes to withdrawn their consent for participation in the study.

11.0 TREATMENT OF SUBJECTS

The aim of all AF treatment is a complete bi-atrial MAZE IV procedure. [redacted]

Based on the type of concomitant surgery or patient presentation, it is recognized that there may be situations in which some lesions are not able to be performed safely. [redacted]

Mandatory Lesions - A protocol deviation will be documented for any **mandatory** left sided lesion that is either not performed or performed without utilizing the energy source(s) as described in Table 4.

Recommended and Optional Lesions - - A clinical justification must be provided for any **recommended or optional lesions** that are either not performed or performed using an energy source that is different than the energy source(s) as described in Table 4. Protocol deviations will be required if a clinical justification is not provided. . Note: Surgeon's preference is not considered to be a clinical justification.

The investigator should refer to the IFU for details on the product, preparation and usage.

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12.1 Repeat Ablation and/or Cardioversion Procedures

All information regarding any repeat catheter ablations (reason for the re-do as well as location) or any cardioversions will be collected and documented in the CRF. The most prevalent post-procedure rhythm will also be documented and recorded in the CRF.

12.2 Permanent Pacemaker Implantations (PPM)

Information regarding PPM implantation within 30 days of the procedure will be collected and documented in the CRF, including time of implant and reason.

12.3 Standardization of Anti-arrhythmic Drug Use during Follow-up Period

Postoperative use of anti-arrhythmic drugs (AAD) following atrial fibrillation surgery varies significantly among sites and among clinicians at individual sites. In addition, regulation of the medical regimen may be under the direction of the surgeon, the referring clinical cardiologist or both in collaboration. Since no specific data are available to prove efficacy of any given approach, this shall be left up to the discretion and ordinary practice of the investigators. This will not influence the primary efficacy outcomes analysis, since efficacy will be evaluated after AAD washout.

The presence or absence of atrial fibrillation shall be assessed in each treatment subject [redacted]

[redacted]

In addition, some subjects may present for medical care between or at scheduled visits, at which time AF may be discovered. If a patient is in AF during the follow-up course, additional attempts at medical management and cardioversion/catheter ablation can be undertaken as medically indicated. However, every effort should be made to discontinue AADs at least 4 weeks (except amiodarone which must be discontinued 12 weeks prior to assessment) prior to the Holter, Zio™ Patch or PPM interrogation evaluations [redacted]. If AADs cannot be discontinued at least four (4) weeks (12 weeks for amiodarone) [redacted] the subject will, by definition not be considered a primary efficacy outcome success.

13.0 ASSESSMENT OF SAFETY

13.1 Adverse Events

During each clinical follow-up, the investigator or designee will determine adverse event (AE) occurrences. An adverse event is any untoward medical occurrence (signs, symptoms, abnormal laboratory findings) in a patient regardless of relationship to the device or procedure. Each adverse event is considered to be either anticipated or unanticipated as described below. The site is required to report all adverse events that occur in the study.

13.2 Anticipated Adverse Events

A variety of complications are expected to occur in subjects undergoing treatment for atrial fibrillation with the AtriCure Synergy Ablation System concomitant with an open-heart procedure requiring cardiopulmonary bypass. These anticipated adverse events are provided in Appendix A.

These events shall also be classified according to the suspected causality by the study investigator. Causality can be attributed to the device, the surgical procedure or to the subject's underlying disease according to the definitions below.

Device Related Adverse Event: An adverse event, which in the judgment of the Investigator, results from use of the AtriCure Synergy Ablation System.

Ablation Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the ablation procedure and is not specifically related to use of the AtriCure Synergy Ablation System.

Surgical Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the surgical procedure to address underlying structural heart disease and is not specifically related to use of the AtriCure Synergy Ablation System or the ablation procedure.

Underlying Disease Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the subject's underlying medical condition and is related to neither the ablation nor structural heart disease surgical procedures nor to use of the AtriCure Synergy Ablation System.

If the Investigator cannot determine the cause of the event, it should be classified as unknown.

13.3 Events that do not require reporting to the sponsor

For purposes of this study, the following events will not be required to be reported as adverse events to the sponsor, because they are normally expected to occur in conjunction with surgical treatment for non-paroxysmal forms of atrial fibrillation procedures (Maze IV) or are associated with customary, standard care of patients undergoing cardiac surgery:

- Chest pain without associated ECG changes
- Post-operative pain
- Post-anesthesia emesis, nausea, or headache (within 24 hours of procedure)
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction
- Pre - planned future surgical procedures
- Low grade temperature increase (101°F or 38.5°C)
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo.
- Elevated white blood count, outside the standard laboratory normal value, without signs and symptoms of infection
- Post-operative hematocrit decrease from baseline measured in the OR, prior to the first incision, not associated with hemodynamic changes, remaining above 25% and requiring < 3 units PRBC's
- Minor, localized tenderness, swelling, induration, oozing, etc. at surgical site.
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Any blood transfusions during preplanned operative procedures and unrelated to an adverse event.
- Thrombocytopenia: does not become an AE until treatment is administered.
- Atelectasis - collapse of lung tissue affecting part or all of one lung; the alveoli are deflated. This is not considered to be an AE unless treatment other than chest PT is required or it prolongs hospitalization.
- Hyperglycemia - The use of insulin in the post-operative period does not constitute hyperglycemia if during the same hospitalization. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post-operative does not constitute hyperglycemia.
- Pleural effusion is not an event unless treatment with thoracentesis or chest tube insertion is required
- Pericardial effusion without hemodynamic compromise or treatment

- Atrial Fibrillation /Atrial Flutter/Atrial Tachycardia with or without cardioversion. Note: the occurrence of AF is reported as an outcome in the study and documented on a follow up visit CRF.

13.4 Serious Adverse Events

All SAEs must be reported to AtriCure or designee within 24 hours of investigational site knowledge of the event. [redacted]

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is an important medical event which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes

The Investigator at each participating center is ultimately responsible for reporting adverse events (complications) to AtriCure or its designated CRO. Investigators must report SAEs within 24 hours of investigational site knowledge of event occurrence by entering data into the Case Report Form in the electronic database. The Investigator is required to complete the adverse event Case Report Forms at each study visit, if an adverse event occurs. One adverse event CRF must be completed for each adverse event.

All adverse events will be reported to FDA at least annually.

14.0 Clinical Events Committee (CEC)

An independent group of physicians that are not involved in the clinical investigations will act as the Clinical Events Committee (CEC) under the direction of [redacted] The CEC will be responsible for the review and validation of reported potential ENDPOINT adverse events (i.e.: all device/procedure related SAEs) that occur within 30 days post procedure per the CEC Charter. The CEC shall classify each of these adverse events based on severity and association to the device and/or procedure. During the review of the events, the CEC will be blinded to the clinical site as much as possible. The CEC Charter will be developed prior to the start of study enrollment. This charter shall include consistent definitions for each type of event and shall outline the review process.

15.0 MEDICAL DEVICE REPORTING

15.1 Manufacturer Reporting Requirements

The AtriCure Synergy Ablation System is commercially available and subject to FDA Medical Device Reporting (MDR) regulations. These regulations require manufacturers who receive complaints of device malfunctions, serious injuries or deaths associated with medical devices to notify FDA of the incident. AtriCure will comply with the MDR requirements for devices used in this study through the information gathered on the case report forms and source documents obtained from the site. If there is a device malfunction or other observation, the Device Observation CRF requires the Investigator to notify AtriCure immediately and indicate if the observation resulted in an adverse events and indicate if complications are related to the device, procedure or underlying disease. The collective information required on AtriCure MDR procedure forms are designed to comply with time sensitive reporting requirements. AtriCure will submit MDR reports according to 21 CRF parts 803.50 through 803.58.

In the event of an MDR, the site should contact:

AtriCure, Inc.
Complaints/MDR Reporting
[redacted]

16.0 STATISTICAL CONSIDERATIONS

16.1 Statistical Overview

The purpose of this study is to evaluate continued safety and efficacy of the AtriCure Synergy Ablation System during commercial use in real world settings for surgical ablation of non-paroxysmal atrial fibrillation during concomitant cardiac surgical procedures.

16.2 Analysis Populations

The primary analysis population will consist of patients who received the AtriCure Synergy Ablation System for treatment of non-paroxysmal atrial fibrillation in the setting of a concomitant cardiac surgical procedure. Other sub-populations will be detailed in the statistical analysis plan.

The primary study outcomes will also be stratified according to primary cardiac surgical procedure type, e.g.:

(1) CABG

(2) Aortic Valve

(3) Mitral Valve

(4) Tricuspid Valve, and

(5) Multiple procedures

We will stratify enrolled subjects by type of primary cardiac surgical procedure to assure a reasonable precision of the estimate for serious device or procedure related SAEs within each specified stratum.

In addition, primary study outcomes will be stratified by “new users” versus “existing users”. A “new user” is defined as a site that has not performed the Maze IV procedure in the past, or has not performed the procedure with the AtriCure Synergy Ablation System. An “existing user” is defined as a site that performs the MAZE IV procedure using the AtriCure Synergy Ablation System.

16.3 Sample Size Calculations and Assumptions

The study will enroll up to 390 subjects at 50 North American centers. This number of subjects shall provide an adequate sample to fully assess the outcome of the procedure within a broad population.

The patient sample size for this study was derived to establish that the rates for the primary outcomes of 30-day serious device and ablation procedure related AE and 3-year efficacy success rates are within the pre-established reference rate bounds. This number of subjects shall provide an adequate sample to fully assess the outcome of the procedure within a broad population and should supply a sufficient number of subjects for both 30 day safety evaluation (>333 subjects at 30 days) and long term efficacy evaluation (>275 subjects at 3 years). Should the statistical power be sufficient with fewer than 390 subjects (at least 333 subjects at 30 days), PAS will stop recruitment early and continue to follow those subjects currently enrolled.

16.4 Safety

The primary safety objective of the ABLATE Post Approval Study (ABLATE PAS) is to demonstrate that the serious device and ablation procedure related AE rate (excluding pacemaker implantation) within 30 days or prior to discharge (whichever is later) of the AtriCure Synergy Ablation System is no worse than a performance goal derived from the non-paroxysmal AF subject cohort of the combined AtriCure IDE ABLATE and ABLATE AF clinical trials.

The rate of serious device or ablation procedure related adverse events (excluding pacemaker implantation) within 30 days or prior to discharge (whichever is later) in the non-paroxysmal AF subject cohort of the combined AtriCure IDE ABLATE and ABLATE AF clinical trials was 6.25% (4/64).

The acceptable upper limit of the serious device and ablation procedure related AE rate for the ABLATE PAS trial (i.e. the performance goal) is established at 10%.

The primary safety hypotheses for this study are stated as follows:

$H_0 : \pi_{PAS\_SAFETY} \geq 10\%$
$H_1 : \pi_{PAS\_SAFETY} < 10\%$

Using a one-sided exact binomial test for proportions at the 0.05 overall level of significance, a total of 333 subjects are required to demonstrate that the 30 day serious device or procedure related AErate

(excluding pacemaker implantation) in subjects treated with the AtriCure Synergy Ablation System is < 10% (the performance goal) with 80% power. This calculation was completed using PASS 2008 Power and Sample Size Software by NCSS.

A maximum of 15% Loss to Follow-Up (LTFU) is anticipated through 30 days, as such the sample size for enrollment is increased to 390 subjects to ensure a minimum of 333 subjects are available for assessment of the primary safety endpoint through 30 days. Should LTFU be less than 15%, enrollment will stop early given the safety endpoint is powered to at least 80%.

16.5 Efficacy

Based on data collected from the non-paroxysmal AF subject cohort of the AtriCure IDE ABLATE clinical trial it is estimated that approximately 55-60% of patients treated with the AtriCure Synergy Ablation System will be free of AF while off AADs at 2-3 years follow-up, where free of AF is defined as no episode of atrial fibrillation, atrial flutter or atrial tachycardia lasting longer than 30 seconds. This estimate is based on the 57.8% success rate (26/45) seen at an average follow-up time of 20 months in the subset of non-paroxysmal AF subjects treated under the AtriCure IDE ABLATE trial.

[redacted]

[redacted]

The primary efficacy hypotheses for this study are stated as follows:

[redacted]

Assuming a success rate of 57.8% and a loss to follow-up that only leaves 250 of the initial 390 patients evaluable at 3 years, this test of efficacy superiority with a significance level of 0.05 can [redacted]. Since this is even greater than [redacted], the ABLATE PAS sample size is driven by the safety primary endpoint.

16.6 Statistical Analyses

Primary Analysis

Serious device and ablation procedure related AE rates and confidence intervals will be summarized at discharge, 30 days, and 1-year with a hypothesis test performed on the cumulative 30 day serious device

and ablation procedure related AE rate. The primary safety hypothesis test will be conducted using a one-sided exact binomial test for proportions at the 0.05 overall level of significance.

The efficacy outcome rate of freedom from AF, off antiarrhythmic drugs along with confidence intervals will be summarized at 1, 2 and 3 years (i.e. 12. 24, 36 month follow-up), with a hypothesis test performed on the 3-year success outcome. The primary efficacy hypothesis test will be conducted using a one-sided exact binomial test for proportions at the 0.05 overall level of significance.

Secondary Analysis

Secondary outcomes will be summarized for the analysis population and certain sub-populations. Two-sided 95% confidence intervals will be calculated for all presented rates. Descriptive analyses will be provided for patient demographics, clinical device/procedural success, medical histories, and co-morbidities. Logistic regression analyses may be used to screen a wide range of parameters for their association with some outcomes.

Procedures to Account for Missing Data

Reasonable efforts will be made to obtain complete data for all patients; however, missing observations will occur due to patients lost to follow-up or noncompliance with required assessments. The reasons for missing data will be evaluated (e.g. patient is deceased, lost to follow up, missed visit, etc.). In addition, the distribution of prognostic factors between patients with data and those without data will be examined to evaluate any potential sources of bias.

Any missing observations will be described in detail and evaluated for assessment of possible bias. For the primary analysis of safety and efficacy outcomes, missing data will be imputed using multiple imputation methods (e.g. SAS PROC MI). Additional sensitivity analyses of missing data including 1) considering everyone who was a failure at last visit also a failure at 3 years and multiple imputation on everyone who was a success at last visit, 2) including everyone LTFU as a failure and 3) a tipping point analysis will also be performed.

17.0 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Protocol Deviations

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study patient who does not meet all of the inclusion/exclusion criteria specified in the protocol and missed study visits without documentation. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, ISO guidelines, Good Clinical Practices, and any conditions of approval imposed by their IRB.

All deviations are reviewed and assessed for their impact on patient safety by AtriCure or designee. The site PI and study staff is responsible for knowing and adhering to their IRB/EC reporting requirements.

The protocol deviations for this protocol consist of, but not limited to the following:

- Failure to obtain patient's informed consent prior to any study-related activities and the index procedure
- Use of other approved devices for the ablation procedure or MAZE IV procedure, or lesion set deviations.
- Failure to conduct protocol required clinical follow-ups
- Failure to conduct protocol required clinical follow-ups within time windows
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in termination of the site's study participation. Patients already enrolled at these sites will continue to be follow per the clinical protocol.

17.2 Investigator / Investigational Site Training

AtriCure and/or designated CRO will be responsible for providing training to the investigator and appropriate clinical site personnel.

17.3 Monitor Training

AtriCure and/or designated monitors will be trained appropriately to monitor study progress including but not limited to the protocol and CRFs.

17.4 Study Monitoring

A study specific monitoring plan will be conducted to ensure protocol compliance and applicable regulatory requirements.

Clinical monitors will verify patient data and ensure compliance with GCP, clinical protocol and other study requirements, according to the guidelines set forth in the monitoring Standard Operating Procedures (SOP) and ISO 14155 guidelines to be utilized for the study.

17.5 Site Monitoring

AtriCure or designee may conduct periodic compliance assessments at various study sites. AtriCure or designee may request access to all trial records including source documentation for inspection and photocopying during a compliance assessment. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

17.6 Regulatory Agency Inspection

In the event that an investigator is contacted by a regulatory agency regarding this trial, the investigator will notify AtriCure or its designee immediately. The investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The

investigator must provide AtriCure or designee with copies of all correspondence that may affect review of the current trial (e.g., Form FDA 483, Inspectional Observations and Warning Letters). AtriCure may provide needed assistance in responding to regulatory audits.

18.0 ETHICS/PROTECTION OF HUMAN SUBJECTS

18.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997), the Declaration of Helsinki, CIOMS, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002).

18.2 Institutional Review Board/Ethics Committee

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate Ethics Committee(EC)/Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are placed into use.

18.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

18.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and AtriCure and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the AtriCure may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

19.0 DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), [redacted] and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

19.1 Investigator Records

Investigators will maintain complete, accurate and current study records. Records shall be maintained during the clinical study and for two years after the later of the date on which the study is terminated or completed, or the date the records are no longer required to support FDA approval of the device. Investigator records shall include the following materials:

- **Correspondence**: Documentation of all verbal and written correspondence with FDA, AtriCure, the Clinical Monitor, the Clinical Events Committee (CEC), and other investigators regarding this clinical study or any patient enrolled therein.
- **Subject records**: Signed informed consent forms, copies of all completed Case Report Forms and supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each subject to the device. Informed consent must comply with FDA regulations (21 CFR, part 50).

- **Investigational Plan (Clinical Study Protocol)**: A current copy of the Clinical Study Protocol including Instructions for Use of the AtriCure Synergy Ablation System and blank case report forms.
- **Institutional Review Board (IRB)/Ethics Committee (EC) Information**: All information pertaining to IRB/EC review and approval of this clinical study including a copy of the IRB/EC letter approving the clinical study, a blank informed consent form approved by the IRB/EC, and certification from the IRB/EC Chairman that the IRB/EC complies with FDA regulations (21CFR, Part 56)/regulatory body regulations, and that the IRB/EC approved the clinical study protocol based on the Report of Prior Investigations.
- **Investigator Agreements**: Copies of signed Investigator, Co-investigator and Sub-Investigator Agreements with accompanying curriculum vitae.
- **Other**: Any other records that may be required by applicable state or federal laws.

19.2 Investigator Reports

The Investigator will prepare and submit the following reports:

- **MDR:** Medical Device Reporting of all events related to the device or device malfunctions.
- **Withdrawal of IRB Approval**: Withdrawal of approval shall be reported to AtriCure or designee within five working days. The Investigator will provide a written report of the reason(s) approval was withdrawn.
- **Progress Reports**: The Investigator will submit progress reports to AtriCure or designee in the form of completed Case Report Forms. The same forms will be used at all Investigative Centers for the recording of data on the findings of follow-up evaluations and complications. In addition, the Investigator may be asked to submit progress reports to AtriCure or designee and the reviewing IRB that include the number of study subjects, a summary of follow-up data and complications and a general description the study progress.
- **Final Report**: The investigator shall submit a final report within three months of termination or completion of the study or that Investigator's participation in the study, to AtriCure or designee and the IRB.
- **Other Reports**: Upon the request of FDA, the reviewing IRB, or AtriCure or designee, the Investigator will provide accurate and timely information about any aspect of the clinical study.
- **Deviations from the Study Protocol**: The Investigator shall notify AtriCure or designee and the reviewing IRB of any deviation from the Clinical study protocol intended to protect the life or physical well being of a patient in an emergency. Such notice shall be given as soon as possible, but in no event later than five working days after the emergency occurred. Except in such an emergency, prior approval of AtriCure is required for any deviation from the Clinical study protocol. Approval from the FDA and the reviewing IRB is also required if these changes or deviations are expected to affect the rights, safety or welfare of human subjects.

19.3 Data Management Responsibilities

Electronic Case Report Forms are used for the collection and recording of data at all Investigative Centers. Investigators are responsible for the timely completion and updating the electronic case report form database (enrollment form should be completed within 24 hours of the concomitant surgical procedure; follow up visits should be completed within 5 working days of the corresponding study visit. SAEs to be reported within 24 hours of knowledge of the event).

Incoming data are reviewed to identify inconsistent or missing data and adverse events. Data issues will be addressed within the EDC system with the investigative Centers and/or during site visits. All hard copy forms and data files will be secured to ensure confidentiality.

19.4 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

20.0 PROTOCOL AMENDMENTS

Approved protocol amendments were provided to investigators by AtriCure or its designee prior to implementation. The site Investigator was responsible for notifying the IRB of the protocol amendment with administrative changes or obtaining IRB approval of the protocol amendment with changes in patient care or safety, according to instructions provided by AtriCure or its designee with the protocol amendment. Institutional Review Board acknowledgements and approvals must be documented in writing prior to implementing protocol amendments. Copies of this documentation must also be provided to AtriCure or its designee.

21.0 TERMINATION OF STUDY OR STUDY SITE PARTICIPCATION

AtriCure may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All patients already enrolled will continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the final follow-up visit of the last enrolled patient.

AtriCure reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum patient enrollment requirements

- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to AtriCure.

22.0 LITERATURE REFERENCES

1. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints and Research Trial Design. 2012 Heart Rhythm Society
2. Peters NS et al., Atrial Fibrillation: strategies to control, combat and cure. Lancet; 2002:359:593-603
3. American Heart Association. Heart Disease and Stroke Statistics – 2006 Update. Circulation. 2006; 113:e85-e151.
4. Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence, Yoko Miyasaka, Marion E. Barnes, Bernard J. Gersh, Stephen S. Cha, Kent R. Bailey, Walter P. Abhayaratna, James B. Seward and Teresa S.M. Tsang. Circulation 2006; 114; 119-125.
5. Brown, DL et al "Projected costs of ischemic stroke in the United States" Neurology. 2006; 67:1-1.
6. Di Tullio MR, Homma S. Mechanisms of cardioembolic stroke. Curr Cardiol Rep. 2002;4:141-148

Appendix A: Adverse Event Definitions

Acute Coronary Syndrome (ACS): Any constellation of clinical signs or symptoms suggestive of AMI (acute myocardial ischemia) or UA (unstable angina). This syndrome includes patients with AMI, STEMI (ST-Segment Elevation Myocardial Infarction), NSTEMI (non-ST-elevation myocardial infarction), enzyme-diagnosed MI, biomarker-diagnosed MI, late ECG-diagnosed MI, and UA. This term is useful to generically refer to patients who ultimately prove to have 1 of these diagnoses to describe management alternatives at a time before the diagnosis is ultimately confirmed.

Acute respiratory distress syndrome (ARDS): A failure of the respiratory system characterized by fluid accumulation within the lung that causes the lung to stiffen. This condition must be confirmed by radiological evidence, or lung biopsy, or the need for prolonged positive pressure ventilation.

Air Embolism: An inadvertent introduction of air or gas to the vasculature which requires medical treatment.

Allergic Reaction: An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general collapse (anaphylaxis).

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to <21 or Hgb < 7. 5%. Any documented anemia event requiring ≥ 3 units PRBCs will be considered an SAE.

Angina: Chest pain or discomfort due to myocardial ischemia. Typical angina is uncomfortable pressure, fullness, squeezing or pain in the center of the chest. The discomfort also may be felt in the neck, jaw, shoulder, back or arm. Angina should be confirmed by evidence of coronary artery blockage such as electrocardiographic changes, positive imaging study (radioisotope scanning), coronary angiography or cardiac MRI.

Arrhythmia (other than AFIB)

- **Bradycardia:**
- *Significant Bradycardia is symptomatic bradycardia (with heart rate less than 60 and symptoms attributed to the slow rate) or extreme bradycardia (persistent rates less than 40 bpm).*
- **Supraventricular tachycardia (SVT)***: Supraventricular rhythm > 100 bpm for > 30 seconds*
  Ventricular tachycardia (VT): A regular heart rhythm originating from the ventricle > 120 bpm and clinically significant. Sustained VT is > 30 seconds or requires intervention.
- **Ventricular fibrillation (VF):**. *An extremely rapid polymorphic ventricular rhythm with essentially no cardiac output.*

Arterial embolism: Angiographic evidence of embolic occlusion in any vascular distribution.

Atelectasis (post surgical): Is a collapse of lung tissue affecting part or all of one lung; the alveoli are deflated. This is not considered to be an AE unless treatment other than Chest PT is required or it prolongs hospitalization.

Atrial Fibrillation: A heart rhythm disorder in which the upper chambers of the heart (the atria) contract very rapidly in a disorganized manner without effective atrial contraction. AF is characterized by the presence of this chaotic uncoordinated electric activity from the atria to the AV node and is associated with irregular ventricular response. The atrial rate can be between 300 to 600 beats per minute.

Atrial Tear/Perforation/Rupture/ Bruise: Any evidence of a tear or damage to one of the atria.

Atrial thrombus: Thrombus formation or detection within the atrium.

Atypical Chest Pain: Located under the sternum, left chest, abdomen, back, or arm and is fleeting or sharp. It is unrelated to exercise, not relieved by rest or the administration of nitroglycerin.

Bacteremia: Presence of viable bacteria in the circulating blood. May be associated with clinical signs/symptoms such as fever but not hemodynamic compromise. Must be confirmed by having one positive blood culture and no subsequent negative cultures.

Bleeding complications:

Bleeding:

Major bleeding Is defines as $\geq$ 3 units of blood transfused in a 24 period

Minor Bleeding Is defined as < 3 units of blood transfused within a 24 hour period

Procedural Bleeding: Bleeding occurring during the procedure requiring 3 or more units of blood transfused.

Major Bleeding: Any bleeding which results in a drop in hematocrit from pre-procedure level which is associated with hemodynamic compromise or which results in a hematocrit of ≤ 25% or blood loss that requires transfusion of 3 or more units of blood.

Coagulopathy: Documented inappropriate coagulation, which leads to the consumption of clotting factors, resulting in the failure of the clotting mechanism at the site of bleeding.

Disseminated intravascular coagulation (**DIC):** Also known as **consumptive coagulopathy**, which leads to the activation of coagulation (blood clotting) mechanisms. This leads to the formation of small blood clots inside the blood vessels throughout the body.

Hematoma: Development of a collection of blood > 5 cm's under the skin requiring transfusion or surgical intervention to resolve.

Intracranial Hemorrhage: Includes all bleeding within the cranium either subarachnoid, intra-parenchymal, or intracerebral.

GI Bleed: Detection of frank blood or hemoglobin in the stool which requires medical intervention including but not limited to transfusion, medication, surgical intervention, prolongation of hospital stay, or re-hospitalization**.**

Cardiac Arrest: Cardiac arrest is the sudden, abrupt loss of heart function. *Often related to malignant arrhythmia. Results in sudden death unless acutely successfully resuscitated*.

Cardiac Tamponade: The compression of the heart caused by blood or fluid accumulation in the space between the myocardium and the pericardium. Cardiac tamponade (also referred to as pericardial tamponade or tamponade) is associated with a hemodynamic profile characterized by equalization of right and left heart diastolic pressures and/or pulsus paradoxicus (a > 15cm drop in blood pressure during inspiration).

Coronary Artery Injury: Damage to the artery caused during surgery requiring repair.

Cardiac Valve Injury: Damage to any cardiac valve resulting from the index surgical procedure.

Cardiogenic Shock: Patient presents with SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids and / or requiring intravenous pressor agent or an intraortic balloon pump (IABP).

Congestive Heart Failure (CHF): A clinical syndrome caused by heart disease, characterized by breathlessness and abnormal sodium and water retention, and resulting in edema. This term is used when there is congestion of pulmonary or systemic vascular beds.

Death: All cause mortality. Death is not an adverse event, it is an outcome. The Adverse Event is what caused the death. Death (within the first 30 days postoperative or >30 days if procedure related).

Sudden Death: Cardiac arrest which is unexpected and occurs within minutes of the onset of symptoms.

Damage to intra-thoracic structures other than the heart (e.g., lungs, trachea, esophagus, aorta/arteries, vena cava/veins, etc.): Any evidence of puncture/dissection/perforation or damage to any non-cardiac structure within the thoracic cavity requiring intervention.

Deep Vein Thrombosis (DVT): Unilateral lower extremity swelling, redness, pain with confirmation by Doppler tests of obstructed venous flow in that extremity. DVT occurring within 30 days of the surgical procedure shall be considered procedure related.

Diaphragmatic paralysis: May be unilateral or bilateral. May be caused by injury to the phrenic nerve as a result of *trauma* to the *thoracic* cage.

Drug Reaction: Adverse event related to a drug reaction to the anesthesia or intercostal blocks (pain medications) used during the surgical procedure.

Endocarditis: An infection associated with classic signs of endocarditis (positive blood cultures, fever, red blood cell casts in urine, splinter hemorrhages in finger nails, roof of mouth, lesions on retina, etc) associated with a vegetation inside the atrium or on a valve which may be confirmed on echo cardiography.

Esophageal Fistula: Abnormal passage communicating with the esophagus (for the purposes of this protocol- likely resulting from an esophageal rupture).

Esophageal rupture: Any evidence of puncture/dissection/perforation or damage to the esophagus.

Fever: A temperature > 101°F / 38.5°C not related to a culture positive infection.

General Discomfort: Physical or psychosocial signs or symptoms commonly associated with hospitalization that are investigated and determined to require minor (i.e. aspirin, non-narcotic medication) or no, treatment.

Headache: Aching or pain that occurs in one or more areas of the head, face, mouth, or neck. Headache can be chronic, recurrent, or occasional. The pain can be mild or severe enough to disrupt daily activities.

Hemoptysis: A cough that produces bloody sputum.

Hemolysis: The breakdown of red blood cells.

Heparin-Induced Thrombocytopenia (HIT): A 50% or greater fall in the platelet count from the postoperative peak[1] which may be confirmed with + antiplatelet antibodies.

Hepatic Failure: A clinical condition that results from severe and extensive damage of liver cells leading to failure of the liver to function normally and can induce mental confusion of various degrees. Liver failure is described as the combination of hyperbilirubinemia (Total Bilirubin >2), Coagulopathy with INR level greater than the upper limits of normal (in the absence of Coumadin treatment) and Hypoalbuminemia, with an albumin <3.

Hyperglycemia: The use of insulin in the post op period does not constitute hyperglycemia if during the same hospitalization. An Elevated blood sugar of less than 250 during the first 48 hours post op does not constitute hyperglycemia.

Hypertension: Systolic BP > 140 mmHg, or diastolic > 90 mmHg requiring specific medical therapy.

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[1] Warkentin TE, et al. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. Arch Intern Med. 2003 Nov 10;163(20):2518-24.

Hypotension: Low blood pressure requiring medical intervention or treatment with medication.

Infection: The following are the categories for infections:

- **Deep Sternal:** Involving muscle, bone, and/or mediastinum.
- **Thoracotomy Site:** Involving a thoracotomy or parasternal site.
- **Lung:** Involving airways associated with intubation or other respiratory causes.
- **Leg:** Involving a leg vein harvest site.
- **Chest tube:** Involving the chest tube insertion site
- **UTI:** Involving the urinary tract.
- **Pacemaker site:** Involving the incision line created for pacemaker placement
- **Or Systemic Infection:** Bloodstream infection caused by bacteria.

Each type of infection should be classified as either Major or Minor as outlined below:

- **Infection Major:** Life threatening or requiring surgical intervention.
- **Infection Minor:** Temperature > 101°F / 38.5°C or higher and a positive culture (e.g., tissue, urine, etc.). Easily eradicated requiring a brief course of antibiotics.

Leukopenia: Leukopenia is defined as leukocyte count of $<3.5 \times 10^9$/liter for more than 3 days.

Limb ischemia: Limb ischemia is manifested by pain in an extremity at rest, associated with non-healing wounds and gangrene. Limb ischemia should be confirmed by diagnostic imaging studies.

Medication Reaction: An unwanted or harmful side effect experienced following the administration of a drug or combination of drugs and is suspected to be related to the drug.

Multi-organ failure: Failure of more than one organ due to shock or sepsis. This requires volume and inotropic support and has a high incidence of death.

Myocardial infarction: Myocardial damage detected either by electrocardiographic changes including ST segment elevation, laboratory evaluation (e.g., elevated levels of serum CPK-MB, troponin-I) or cardiac imaging studies (echocardiographic images showing reduction in ejection fraction from the pre-operative level).

Nausea: The unsettling feeling in the stomach that accompanies the urge to vomit.

Neutropenia: Neutropenia is defined as ANC <1000 per mm^3 for more than 3 days.

Ogilvie Syndrome/Acute Colonic Pseudo-Obstruction (ACPO): Clinical disorder with the signs, symptoms and radiographic appearance of an acute large bowel dilatation with no evidence of distal colonic obstruction.

Pain: An unpleasant sensation occurring in varying degrees of severity as a consequence of injury, disease, or emotional disorder.

Pain (Persistent Chest Pain): Post discharge surgical incisional pain, not angina.

Pericardial Tamponade: See Cardiac Tamponade.

Pericarditis: Infection of the pericardium which may or may not require re-operation.

Peripheral Edema: The swelling of tissues, usually in the lower limbs, due the accumulation of fluids.

Pleural Effusion: Accumulation of fluid in the pleural space evidenced by x-ray, echocardiography, CT Scan or other appropriate diagnostic technique and which requires drainage.

Pneumothorax: Air in the thoracic cavity associated with partial collapse of a lung with chest tube drainage.

Pneumonia: An inflammation of the lungs caused by an infection. This condition must be confirmed by radiological evidence, positive sputum culture, or significant improvement of the condition following antibiotic treatment.

Pulmonary edema: Pulmonary edema is present if there is fluid accumulation in the lungs caused by backpressure in the lung veins. This condition must be confirmed by radiological evidence or lung water measurements.

Pulmonary embolism: an obstruction of a blood vessel in the lungs, usually due to a blood clot, which blocks a pulmonary artery.

Pulmonary hypertension: Patient has mean pulmonary artery pressure that is greater than 25 mmHg at rest and/or greater than 30 mmHg during exercise as measured by right heart catheterization.

Pulmonary vein stenosis: Defined ≥70% stenosis of one pulmonary vein or ≥50% stenosis of more than one vessel. PV stenosis is manifest as dyspnea at rest, may be associated with hemoptysis and must be confirmed by imaging studies of the pulmonary veins (using CT or MRI).

Pulmonary vein stenosis, suspected: Any patients exhibiting mild or suspected pulmonary vein stenosis (defined as >40% stenosis of one vein or >30% in more than one vein) shall undergo additional imaging studies at 12 months or as needed.

Pseudo-aneurysm: Disruption of the arterial wall characterized by an outpouching or pocket with swirling, flowing blood outside of the confines of the arterial lumen.

Respiratory failure: Need for mechanical ventilation beyond 48 hours of completion of surgical procedure(s), or the need for re-intubation and ventilator support occurring at any time within 30 days of the surgical procedure, outside the setting of an additional operation.

Renal failure: a.) Increase of > 2.0 mg/dl in serum creatinine from any previous value or, b.) ≥ 50% increase over baseline to a level that is ≥ the upper limit of normal which may require dialysis. .

Reoperation: A repeat operation for the same condition in the same patient or to resolve an adverse event resulting from the initial operation. Reoperation is not an adverse event – it is an outcome – the reason for reoperation is the adverse event.

Restrictive (constrictive) pericarditis: A *chronic* form of *pericarditis* in which the pericardium is rigid, thickened, scarred, and less elastic than normal. The pericardium cannot stretch as the heart beats, which prevents the chambers of the heart from filling.

Retroperitoneal bleeding: Documented collection of blood in the retroperitoneum or by CT/MR.

Sepsis: Positive blood cultures associated with cardiovascular collapse and signs and symptoms of multiorgan failure.

Septicemia: Positive blood cultures.

Seizures: Sudden, uncontrolled muscle spasms with or without loss of consciousness resulting from brain electrical activity.

Sick sinus syndrome: Also called **sinus node dysfunction**, is a group of abnormal heart rhythms (arrhythmia) presumably caused by a malfunction of the sinus node, the heart's primary pacemaker, *often resulting in the combination of sinus bradycardia alternating with rapid supraventricular rhythms such as afib with rapid ventricular response, as tachycardia-bradycardia syndrome*

Stroke (permanent disability): A loss of brain function that occurs when the blood supply to any part of the brain is interrupted, resulting in tissue death or that which occurs with cerebral hemorrhage with clinical sequelae lasting more than 24 hours. Clinical signs/symptoms of neurological deficit as determined by standard comprehensive neurological examination, neurological imaging (CT scan or MRI) or autopsy.

May be further categorized as:

- **Ischemic Stroke:** Neurologic deficit attributed to thromboembolic event.
- **Hemorrhagic Stroke:** Neurologic deficit meeting the study definition for Stroke that is attributed to bleeding into brain tissue, epidural, subdural, or subarachnoid space; or a combination of these sites.

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Thromboembolism: *Formation of a thrombus (*masses composed of insoluble fibrin, deposited platelets, accumulating WBCs, and entrapped RBCs*) that obstructs vascular blood flow locally and detaches and embolizes to occlude blood flow downstream. Diagnostic confirmation should be made with angiography or ultrasound.*

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack (TIA): A neurological deficit lasting less than 24 hours and if an imaging study is performed showing no evidence of infarction.

Unstable Angina: Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Vasovagal Reaction: Reflex stimulation of the vagus nerve causing slowing of the heartbeat, decreased blood pressure, *lightheadedness or syncope,* etc. and requires treatment consisting of any of the following: (a) > 1 liter of IV fluids; (b) postural changes; (c) pacing intervention; or (d) administration of atropine.

Ventricular tear / perforation / bruise /rupture: Any evidence of puncture/dissection/ perforation or damage to the ventricle. The AtriCure Bipolar System is not intended to be used in the ventricle. Care should be taken during introduction of the device on the left side of the heart so that the clamps and shaft of the device do not come in contact with the ventricle and cause disruption of the ventricular tissue.

Wound dehiscence/delayed wound healing: Not associated with infection.