AtriCure, Inc.

7555 Innovation Way
Mason, Ohio 45040

DEEP Pivotal Study
CLINICAL STUDY PROTOCOL

Study Number: CP2014-1
Revision: H / 11May2021

Regulatory Classification:	Investigational Device Exemption Significant Risk
Name of Finished Product:	AtriCure® Bipolar System AtriClip PRO® LAA Exclusion System
Sponsor's Medical Monitor:	Sydney Gaynor, MD Medical Director of Clinical Education, Clinical AtriCure, Inc. 7555 Innovation Way Mason, OH 45040
Principal Investigators:	Kenneth Ellenbogen, MD Vigneshwar Kasirajan, MD Ali Khoynezhad, MD

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 ISO14155:2020) 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, MHRA, etc.).

Rev.	DCN Number	Revision Summary
H	DCN-2021-0675	Protocol revised due to FDA design considerations. See redlines.

INVESTIGATOR SIGNATURE

I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met;
- Conduct the clinical study in accordance with this protocol, including applicable local/state laws and regulations;
- Provide a copy of Financial Disclosure form that summarizes financial interest in the AtriCure Bipolar System and the AtriClip PRO LAA Exclusion System;
- Adhere to the publication policy of AtriCure, as stated in the Clinical Study Agreement (CSA), for data collected during this study;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments;
- Complete all Case Report Forms and study documentation and relevant imaging assessments (as required) promptly to the Sponsor, AtriCure, Inc., or its authorized representatives;
- Store all investigational products according to the labeling and Instructions for Use (IFU) in a secure area to prevent unauthorized access or use.
- Propose to the sponsor any appropriate modification(s) of the protocol or investigational device, or of the use of the investigational device.

I will ensure that the IRB/EC review complies with governmental requirements and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to human subjects.
I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the sponsor and government agencies.

Investigator Signature: I have read and understood the contents of this protocol. I agree to follow and abide by the guidelines set forth in this document.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Please return a signed copy to:
Denise Breiner, MBA
Director, Clinical Affairs
AtriCure, Inc. (Sponsor)
7555 Innovation Way
Mason, Ohio 45040

PLEASE RETAIN A COPY FOR YOUR STUDY RECORDS

SPONSOR SIGNATURES

Protocol Name:	DEEP Pivotal Study
Protocol Number:	CP2014-1
Protocol Title:	Pivotal Study Of A **D**ual **E**picardial & **E**ndocardial **P**rocedure **(DEEP)** Approach for Treatment of Subjects with Persistent or Long Standing Persistent Atrial Fibrillation with Radiofrequency Ablation
Investigational Device:	AtriCure Bipolar System and AtriClip PRO LAA Exclusion System

Approvals:

Nfii Ndikintum Date
Vice President, Clinical Affairs and Biometrics
AtriCure, Inc.

Denise Breiner Date
Director, Clinical Affairs
AtriCure, Inc.

Dennis Hong Date
Vice President, Regulatory Affairs
Atricure, Inc.

Ken Frazier Date
Sr. Director, Clinical Development
AtriCure, Inc.

Robert Buehner Date
Manager, Clinical Affairs & Data Management AtriCure, Inc.

Sydney Gaynor, MD Date
Medical Monitor
AtriCure, Inc.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title:	Pivotal Study Of A **D**ual **E**picardial & **E**ndocardial **P**rocedure **(DEEP)** Approach for Treatment of Subjects with Persistent or Long Standing Persistent Atrial Fibrillation with Radiofrequency Ablation
Principal Investigators:	Kenneth Ellenbogen, MD Vigneshwar Kasirajan, MD Ali Khoynezhad, MD
Short Title:	DEEP Pivotal Study
Regulatory Classification:	Investigational Device Exemption Significant Risk
Indication:	The AtriCure Bipolar system is indicated for the treatment of subjects with symptomatic drug refractory persistent or longstanding persistent atrial fibrillation in a minimally invasive endoscopic or open ablation procedure. The AtriClip PRO LAA Exclusion System is indicated for occlusion of the heart's Left Atrial Appendage in a minimally invasive endoscopic or open procedure.
Objective(s):	The objective of this study is to establish the safety and effectiveness of a dual epicardial and endocardial ablation procedure for patients presenting with Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation utilizing the AtriCure Bipolar System and AtriClip PRO LAA Exclusion System in an endoscopic or open ablation procedure, followed by an endocardial mapping and ablation procedure utilizing commercially available RF based, ablation catheters. The following catheters are RF based, irrigated, power controlled, ablation catheters for endocardial lesions and are approved for use in the left atrium: • BioSense Webster ThermoCool Product line (Navistar Thermocool Catheter, Biosense Webster EZ Steer Thermocool Catheter Nav, Thermocool SF Catheters, or BioSense Webster Thermocool SmartTouch) • Abbott (St. Jude) TactiCath Quartz Catheter Product line (TactiCath Quartz Catheter, TactiCath Contact Force Ablation Catheter, Sensor Enabled) The endocardial procedure will be staged to occur after 90 days post epicardial surgical procedure.
Investigational Devices:	AtriCure Bipolar System and AtriClip PRO LAA Exclusion System
Study Design:	Prospective, multicenter, single arm, pivotal study
Number of Subjects (Planned):	Up to 220 subjects will be treated in this study
Investigational Sites:	Up to 35 Sites (30 US and 5 OUS)

Patient Population:	Patients with Persistent or Long Standing Persistent Atrial Fibrillation defined in accordance with the Heart Rhythm Society (HRS) 2012 AF expert consensus statement (2012) ***Persistent***: Continuous AF, which is sustained beyond seven days, or lasting greater than 48 hours and less than seven days but necessitating pharmacologic or electrical cardioversion. ***Longstanding Persistent***: Continuous AF of greater than 12 months' duration.
Inclusion Criteria:	Subjects satisfying the following inclusion criteria will be considered the screening population and will be eligible for participation in this study: 1. Patient is willing and able to provide written informed consent. 2. Patient is ≥18 years of age and ≤ 75 years of age at time of consent. 3. Patient has symptomatic (e.g., palpitations, shortness of breath, fatigue) Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation refractory to a minimum of one Class I or Class III AADs. 4. Patient may have had up to two (2) previously failed catheter ablations to treat atrial fibrillation using catheter ablation are eligible, if they present with symptomatic Persistent or Longstanding Persistent AF. Previous catheter ablation must have occurred greater than three (3) months prior to informed consent. 5. Patient is willing and able to receive all of the study related procedures and attend the scheduled follow-up visits.
Exclusion Criteria:	Subjects will be excluded from the study for any of the following: 1. Patient has a documented history of continued AF >10 years. 2. Patient has refractory hypertension, defined as systolic (>150 mm Hg) or diastolic (> 90 mm Hg) blood pressure that remains uncontrolled despite sustained therapy. 3. Patient has a documented history of pulmonary hypertension (Class III or IV with a mean pulmonary artery pressure >40 mm Hg). 4. Patient exhibits pulmonary vein stenosis in one or more of the pulmonary veins >50 % stenosis. 5. Patient has had an EP catheter ablation procedure to treat atrial fibrillation within 3 months prior to signing consent. 6. Patient is pregnant or lactating or plans on becoming pregnant within the next 2 years. 7. Patient has a medical condition with less than 5 years life expectancy. 8. Patient has undergone prior cardiothoracic surgery (lungs or mediastinum). 9. Patient had previous thorax trauma which resulted in a pneumothorax or hemothorax. 10. Patient has sleep apnea and is non-compliant to current regimen of treatment, i.e., CPAP. 11. Patient is on home oxygen therapy or has moderate to severe Chronic Obstructive Pulmonary Disease (COPD) (FEV1/FVC < 70% predicted) or patient is considered intolerant to single lung ventilation.

12. Patient has NYHA Class IV heart failure.
13. Patient has an uncorrected, reversible cause(s) of atrial fibrillation (e.g., hyperthyroidism, electrolyte imbalance).
14. Patient is currently being treated for arrhythmias other than atrial fibrillation (AF) or atrial flutter.
15. Patient has documented history of previous catheter ablation with perforation.
16. Patient has documented history of pericarditis, tamponade, or clinically significant pericardial effusion.
17. Patient has evidence of underlying structural heart disease requiring surgical treatment (i.e., valve disease requiring repair or replacement within 12 months following surgical ablation procedure).
18. Patient has evidence of underlying CAD requiring intervention (either surgical, i.e., CABG, or catheter).
19. Patient has an ejection fraction < 30% (based on baseline transthoracic echocardiography or equivalent diagnostic test).
20. Patient has a measured left atrial diameter > 5.5 cm in parasternal long axis view (based on baseline transthoracic echocardiography or equivalent diagnostic tests).
21. Patient suspected to have renal insufficiency based on elevated creatinine and BUN (urea) levels.
22. Patient on renal dialysis.
23. Patient has significant liver disease (e.g., cirrhosis) as evidenced by the following liver function tests: total bilirubin > 2x ULN, in association with AST/ALT (or SGOT/SGPT) > 3x ULN. Note: if the required liver function test results do not exceed specified limits, and the investigator's level of suspicion remains high for significant liver disease, if other clinical evidence of significant liver disease (e.g., documented esophageal varices, hepatic encephalopathy) is present and/or imaging study results consistent with significant liver disease are available, this information should be utilized for exclusion.
24. Patient had a stroke/cerebrovascular accident (CVA) within previous six months prior to signing informed consent.
25. Patient has known carotid artery stenosis greater than 80%.
26. Patient has evidence of significant active infection or endocarditis.
27. Patient is unable or unwilling to undergo TEE.
28. Patient's BMI is >40. The medical history of patients with a BMI between 36 and 40 must be reviewed by the study Principal Investigators prior to treatment of the patient to ensure patient meets acceptable health criteria for the epicardial and endocardial ablation procedures.
29. Patient has presence of thrombus in the left atrium or the left atrial appendage, determined by echocardiography (either at baseline TTE (or equivalent diagnostic test) or intraoperative TEE).
30. Patient has history of blood dyscrasia or clotting disorder (i.e., Idiopathic Thrombocytopenic Purpura [ITP] or Thrombotic Thrombocytopenic Purpura [TTP]).
31. Patient has contraindication to anticoagulation that in the opinion of the

	investigator poses undue risk to the patient from participating in the endocardial EP procedure. 32. Patient has a documented thromboembolism within the previous six months prior to signing informed consent. 33. Patient has an atrial myxoma. 34. Patient has a mural thrombus or mural tumor. 35. Patient has a condition or congenital anomaly which prevents required surgical or catheter access. 36. Patient has co-morbid condition that, in the opinion of the investigator, poses undue risk of general anesthesia or port access cardiac surgery. 37. Patient is currently abusing drugs or alcohol. 38. Patient is currently or has participated in a clinical study in the last 3 months prior to signing informed consent. Participation in survey clinical studies with no treatment is not an exclusion criterion. 39. Patient has a psychological disorder that could interfere with provision of informed consent, completion of tests, therapy, or follow-up. 40. Patient has a condition that, in the opinion of the investigator, may jeopardize the patient's well-being and/or the soundness of this clinical study. 41. Patient has a pre-existing esophageal condition that required (or requires) endoscopic therapy or surgical treatment.
Duration of Treatment:	Treated subjects will be assessed for primary safety through 30 days post-epicardial ablation procedure and 7 days post-endocardial procedure. Primary effectiveness will be assessed through 12 months post endocardial ablation procedure. All treated subjects who complete both epicardial and endocardial procedures will be followed through 5 years.
Primary Endpoints:	**Effectiveness:** The primary effectiveness endpoint is freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). Any arrhythmia that occurs within the blanking period or the AAD Optimization period will not be considered a failure. The rhythm status used for evaluation of this endpoint will be derived from regularly scheduled monitoring (i.e., Holter, Zio™-Patch, or 30 second ECG) as well as any symptom driven monitoring that is performed. The following scenarios shall constitute a failure of the primary effectiveness endpoint: 1. Any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds duration that occurs at any time beginning at the 6-month visit and through the 12-month visit. 2. Any previously failed class I or III AAD administered at a dose higher than baseline and between the 6-month visit and the 12-month visit. 3. Any newly introduced class I or III AAD usage beginning at the 6-month visit

and through the 12-month visit.

4. DC cardioversion for AF, atrial flutter, or atrial tachycardia that takes place at any time beginning at the 6-month visit and ending at the 12-month visit.
5. Catheter ablation or surgical treatment for AF, atrial flutter, atrial tachycardia that takes place at any time beginning at the 3-month visit and ending at the 12-month visit.
6. Two or more repeat catheter ablations within the 2nd blanking period.
7. The use of a non-AtriCure study device for creation of any lesions during the surgical epicardial ablation procedure.

For the purposes of this study, atrioventricular nodal reentrant tachycardia (AVNRT), inappropriate sinus tachycardia, and Wolff–Parkinson–White syndrome (WPW) will not be considered procedure failures.

For this study, AtriCure defines failure of an antiarrhythmic drug (AAD) to include ineffectiveness or intolerance of the AAD.

Safety:

The primary safety endpoint is a composite endpoint consisting of any one or more of the following events if they are adjudicated by the CEC to be serious adverse events (SAEs) and related to device/procedures as follows:

1. The AtriCure Bipolar System and/or the AtriClip Pro LAA Exclusion System, within 30 days following the epicardial surgical ablation procedure; or
2. The epicardial surgical ablation procedure within 30 days following the epicardial procedure; or
3. The endocardial index procedure (or a repeat endocardial ablation procedure performed during the blanking period) within 7 days following an endocardial ablation procedure.

Events except as otherwise specified for a particular condition include:

a. death (regardless of cause)
b. stroke
c. transient ischemic attack (TIA)
d. myocardial infarction (MI)
e. pulmonary or systemic embolism
f. pericarditis resulting in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires a new hospitalization, or persists for more than 30 days following the ablation procedure
g. excessive bleeding, defined as one or more of the following:
    i. re-operation to control bleeding within 7 days post-epicardial surgical procedure; or surgery to control bleeding within 7 days post-endocardial ablation procedure, if related to the device or procedure;
    ii. receipt of ≥ 2 units of blood transfused in a 24-hour period during the first 7 days post-epicardial surgical procedure, or within the first 7

	days post-endocardial ablation procedure, if related to the device or procedure; iii. conversion to sternotomy or thoracotomy that requires ≥ 2 units blood to be transfused, or performed to treat hypotension, cardiac arrest, or repair of a cardiac injury. h. wound infection at surgical site requiring re-operation for wound debridement i. atrio-esophageal fistula (from the time of surgical procedure through 1-month follow-up visit) j. permanent phrenic nerve paralysis, defined as paralysis that remains unresolved at the 12-month follow-up visit k. permanent pacemaker implantation that is a direct result of injury to the specialized conduction system (SA node or AV node) during the epicardial surgical ablation procedure l. pulmonary vein (PV) stenosis of >70%, as measured at any time after the endocardial catheter ablation procedure through the 12-month follow-up period m. major vascular access complications, including the development of a hematoma, an arteriovenous fistula, or a pseudoaneurysm requiring intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires a new hospital admission
Secondary Endpoints:	**Effectiveness:** 1. Exclusion of the LAA, defined as defined by lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA. This endpoint will be measured at the 12-Month (Visit 11) (approximately 15 months post AtriClip placement). The AtriClip effectiveness population will be utilized for analysis of this endpoint. 2. Exclusion of the LAA, defined as lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA. The endpoint will be measured intra-procedurally (Visit 2), and at the Endocardial EP Ablation Procedure (Visit 5). The AtriClip effectiveness population will be utilized for analysis of this endpoint. 3. Acute procedural success of epicardial surgical procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins, as well as the "box". 4. Acute procedural success of endocardial catheter procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins and the "box", as well as bi-directional block of the cavo-tricuspid isthmus. 5. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter without AAD, defined as no documented event >30 seconds in duration (or for the entire length of an ECG tracking) with no utilization of AADs beyond the blanking and AAD optimization periods, except as previously failed without an increase in dose. This endpoint will be measured through the 12-month, 2-, 3-, 4-, and 5-year visits (Visits 11-15) via continuous 24-hour ECG

monitor.

6. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter regardless of AAD, defined as no documented event >30 seconds in duration (or for the entire length of a 30 second ECG tracing) regardless of AAD usage. This endpoint will be measured through the 12-month, 2-, 3-, 4-, and 5-year visits (Visits 11-15 via continuous 24-hour ECG monitor).
7. Freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >10 minutes in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).
8. Change in Quality of Life, defined as the total AFEQT score measured at the 12-month follow-up visit minus the score at the baseline visit. The score will be calculated per the AFEQT scoring manual.

Safety:

All secondary safety endpoints are supplemental and intended to provide a more complete picture of the overall safety profile for the DEEP procedure. They will not be tested for labeling purposes.

1. Major surgical events – This will be a composite safety endpoint within 30 days of the epicardial surgical procedure, as otherwise defined in the primary safety endpoint.
2. Major catheter events – This will be a composite safety endpoint within 7 days of the endocardial catheter procedure, as otherwise defined in the primary safety endpoint.
3. 30-day surgical SAEs - This will include all SAEs that occur within 30 days of the epicardial surgical procedure and that are adjudicated to be related to the device or to the procedure.
4. 12-month DEEP SAEs - This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure.
5. Unresolved SAEs – This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure and that are not fully resolved by the 12 months visit. These events shall include any procedure-related deaths, strokes with residual disability, unresolved phrenic nerve damage, or other such events that are adjudicated to have resulted in chronic disability or permanent damage.
6. Any serious adverse event through the 12-month follow-up visit, regardless of attribution.
7. Incidence of stroke or TIA at 12, 24, 36, 48, 60-month visits.
8. Any esophageal injury that meets all of the following criteria: identified post epicardial ablation, adjudicated by core lab to be a thermal injury with perforation, and related to an AtriCure ablation device, through 30-days post epicardial procedure.

Secondary Endpoints – Health Economics:

	All health economics endpoints are exploratory in nature. 9. Utilization of cardioversion, defined as the number of cardioversion events (visits) that a subject had in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits. 10. Hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the number of readmissions in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits. 11. Total length of stay for all hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the sum of the length of stay for each such visit within the last 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits. 12. Emergency Room Visits for AF, atrial flutter, or atrial tachycardia, defined as the number of visits in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.

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KEY PROTOCOL-SPECIFIC ACRONYMS AND ABBREVIATIONS

Acronyms/Abbreviation	Terms
AAD	Antiarrhythmic Drug
AE	Adverse Event
AEF	Atrio-esophageal Fistula
AF	Atrial Fibrillation
EGD	Esophagoscopy
AFEQT	The **A**trial **F**ibrillation **E**ffect on **Q**uali**T**y-of-life Questionnaire
BMI	Body Mass Index
CFAE	Complex Fractionated Atrial Electrogram
CTA	Computed Tomography Angiogram
CTI	Cavo-Tricuspid Line
DEEP	Dual Epicardial Endocardial Procedure
eCRF	Electronic Case Report Form
EC	Ethics Committee
EP	Electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IDE	Investigational Device Exemption
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
LAA	Left Atrial Appendage
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
NOAC	Novel Oral Anticoagulant
OAC	Oral Anticoagulant
OUS	Outside the United States
PI	Principal Investigator
PP	Per Protocol
PPI	Proton-pump Inhibitor
PVI	Pulmonary Vein Isolation
QOL	Quality of Life
SAE	Serious Adverse Event
SOC	Standard of Care
TEE	Transesophageal Echocardiogram (graphy)
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram (graphy)
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal

LIST OF FIGURES

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Schedule of Assessments

Study Activity	Visit 1	Visit 2	Visit 3	Phone Visit	Visit 4	Visit 5	Visit 6	Visit 7 Phone Visit	Visit 8	Visit 9	Visit 10	Symptom Driven Monitor-ing	Visit 11	Visit 12, 13, 14, 15	Phone Visits	Study Exit
	Base-line	Epicardial Procedure	Post-Epicardial Procedure[23]	18 Days (Post Epi)	1 Month follow-up [23]	Endo-cardial Procedure [22, 23]	Post Endo-cardial Procedure	7 Day	1 Month	3 Month [20]	6 Month	Done between 6-12 month visits	12 Month	Year 2, 3, 4, and 5	18, 30, 42, 54 Months	
Visit Timepoint / Window	Up to 45 days		2-3 days post Epi	+/- 2 Days	30 days +7	91-121 days post Epi	1 day post Endo	7 days post Endo +1	30 days post Endo +7	90 days +14	180 days +/- 30	Symptom or Test	365 days + 30	Year +/- 60 days	Approx. 6 Mo post Annual Visit	Exit
Informed Consent	X															
Patient AEF Education	X					X										
Proton Pump Inhibitor (PPI) Prescribed	X[21]					X[21]										
AFEQT Questionnaire	X												X			
Demographics	X															
Medical and Surgical History	X															
NYHA Class	X				X				X	X	X		X			
Neurologic Assessments (NIHSS/mRS)	X		X		X											
Targeted Physical Exam	X		X[26]		X	X		X[13]	X	X	X		X	X[13]		
Height	X															
Weight	X				X	X			X	X	X		X			
Blood Pressure and Heart Rate	X				X	X			X	X	X		X			
Medications Review	X	X[10]	X		X	X	X	X	X	X	X		X	X	X	
AF Classification	X[4]															
Pregnancy Test	X[5]															
30 second ECG-Heart Rhythm Assessment	X[6]	X	X		X	X	X		X	X	X		X			
Blood Collection[1]	X[6]		X		X	X	X		X	X	X		X			
Anticoagulation Testing[2]	X[6]		X		X	X			X	X	X		X			

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Pulmonary Vein Imaging (CT/CTA/MRI)	X[7]				X[12]						X[12]		X[18]			
LAA Imaging (CTA)													X[18]			
Coronary Anatomy Imaging (CT)	X[7]															
LAA Exclusion Analysis[3]						X [(TEE)]							X[(CTA)]			
Lung Function Test	X[8,9]															
Transthoracic Echocardiography (TTE)	X[7]															
Esophagoscopy (EGD)		X[25]	X[25]													
Inclusion/Exclusion Criteria	X	X[11]														
Surgical Procedure/Ablation Procedure Details		X														
LAA Management Details		X														
Transesophageal Echocardiography (TEE)		X[16]				X[19]										
EP Ablation Procedure Details						X										
Adverse Event Assessment		X	X		X	X	X	X	X	X	X		X	X[17]		
Concomitant Arrhythmia Treatment [14]			X		X		X		X	X	X		X	X		
24-Hour Continuous ECG Monitoring/ Arrhythmia Monitoring[15]											X		X	X		
Primary Safety Endpoint					X			X								
Symptom Driven Monitoring											X	X	X			

Study Activity	Visit 1	Visit 2	Visit 3	Phone Visit	Visit 4	Visit 5	Visit 6	Visit 7 Phone Visit	Visit 8	Visit 9	Visit 10	Symptom Driven Monitor-ing	Visit 11	Visit 12, 13, 14, 15	Phone Visits	Study Exit
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Primary Effectiveness Endpoint													X			
Telephone Contact				X[24]				X							X	
Occurrence of AF/AFL/AT – Health Economic Endpoints													X	X		
Study Exit																X

[1] See **Subject Visits** for tests to be conducted at each visit.
[2] Anticoagulation testing to be performed in accordance with institutional SOC depending on subject's anticoagulation therapy.
[3] LAA exclusion verification only for subjects that had the AtriClip placed during Epicardial Surgical Ablation Procedure. These data are submitted to a core lab.
[4] AF Classification Form must be completed and submitted to sponsor for review prior to Epicardial Surgical Ablation Procedure
[5] Urine or serum pregnancy test - females of childbearing potential (**within 7 days prior to the surgical procedure**).
[6] Collection/analysis completed within 7 days of procedure.
[7] Must be conducted within 120 days prior to the Epicardial Surgical Ablation Procedure.
[8] In subjects with a documented history of pulmonary compromise.
[9] Must be conducted within 60 days prior to the Epicardial Surgical Ablation Procedure.
[10] Anticoagulation/antiplatelet therapies administered per SOC.
[11] Intraoperative confirmation that no clot is present in LAA.
[12] CT/MR Imaging performed only if subject exhibits symptoms suggestive of pulmonary vein stenosis. Use same imaging technique performed at baseline imaging to the extent possible.
[13] Only health status will be collected.
[14] For example, cardioversion for subjects in atrial fibrillation per physician discretion.
[15] A Holter or Zio™ Patch will be worn by all subjects.
[16] Conducted prior to surgical procedure to rule out LA/LAA thrombus and post LAA management to confirm exclusion of LAA.
[17] See **Subject Visits 12-15** for details of events of interest to be collected.
[18] CTA imaging of the LAA performed only in those subjects that had the AtriClip placed during the Epicardial Surgical Ablation Procedure. Pulmonary veins will also be

assessed, and CTA will be utilized.

[19] TEE performed at the Endocardial Ablation procedure to confirm LAA exclusion and for confirmation that no thrombi are in the left atrium.

[20] Begin AAD optimization period.

[21] It is required that an acid reducing agent be prescribed 7-daysprior to the procedure and continued for a minimum of 30-days post procedure. [Proton Pump Inhibitors (PPIs) are recommended, however; if the patient cannot tolerate PPIs, an H2 receptor antagonist or other acid reducing agent can be prescribed.]

[22] Reminder to wash patient off AADs leading into Endocardial procedure (see protocol section 5.3.1).

[23] Unscheduled Visit should be conducted in the event of suspected AEF after Visit 3 or Visit 5. If AEF is suspected, endoscopy and/or TEE probes should be avoided, and assessment of AEF symptoms should occur.

[24] Phone call to be conducted Day 18 post Epicardial Procedure to assess if subject is experiencing AEF symptoms.

[25] An esophagoscopy at Visit 2 to be performed prior to placement of access ports for the epicardial procedure. An esophagoscopy at Visit 3 is to be performed 24 to 72 hours post Procedure. If the esophagoscopy reveals esophageal injury, subject reports, images, data and relevant documents will be submitted to a core lab. If in the opinion of the physician the subject requires closer or additional observation, the subject can be seen using “AEF Unscheduled Visit” as often as deemed necessary by the physician.

[26] Includes evaluation for symptoms of AEF.

ETHICS

Independent Ethics Committee or Institutional Review Board
The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

The study protocol, any protocol amendments, Informed Consent Form (ICF), any ICF amendments, and if applicable, any other written information provided to the subjects e.g., subject recruitment advertising, will be reviewed and approved by an or Institutional Review Board (IRB) or Independent Ethics Committee (EC) prior to implementation of any procedures required solely for the purposes of this study. Each Investigator must obtain IRB/EC approval prior to consent of the first subject.

Prior to shipment of the investigation study devices, a signed copy of the IRB/EC approval letter identifying the study and investigational site is required to be submitted to the sponsor signifying study approval.

Each Investigator must also maintain continuous IRB/EC approval. Documentation of approval and renewals must be provided to the Sponsor and filed on site in the Investigator's Regulatory Binder. Additionally, amendments to the protocol will be submitted for review before implementation except when necessary to eliminate apparent immediate hazards to a subject. IRB/EC approval is required to implement protocol amendments or to resume a suspended clinical investigation.

The occurrence of serious or unanticipated Adverse Events (AEs) during the study must be reported to the IRB/EC.

In accordance with the Declaration of Helsinki, a description of the clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

A clinical investigation report will be submitted within one year of the end of the investigation.

The clinical investigation will be concluded when:
- All sites are closed; and
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

Applicable Regulations
Applicable federal regulations include:
- 21 CFR Part 11, 50, 54, 56, and 812;
- ISO 14155:2020;
- International Conference on Harmonization (ICH) Guideline E6 for Good Clinical Practice (GCP) adopted in March 1997;
- Declaration of Helsinki (adopted in 2004); and

- Health Insurance Portability and Accountability Act (HIPAA) regulations, state and local laws and regulations.

Subject Information and Consent

In compliance with FDA regulations, no subject shall be enrolled in an investigation without provision of adequate informed consent. The Principal Investigator is responsible for ensuring that each subject enrolled in the study is given adequate informed consent. Failure to obtain and properly document this process is in violation of the US Code of Federal Regulations, the Declaration of Helsinki, and this study protocol.

The ICF must have the approval of the IRB or favorable opinion of the EC. While some institutions may request for modification of the ICF to satisfy specific institutional requirements, the use of a modified or unique ICF is permitted if it meets the requirement of 21 CFR Part 50 and ISO14155:2020 (as required) and is approved by the Sponsor. Informed consent of all subjects must be documented on an ICF in the primary language of the subject. All translated consent forms need IRB/EC approval. Eligible U.S. subjects should also sign the Health Insurance Portability & Accountability Act form, if not combined with the ICF.

The Investigator or designee shall carry out the Informed Consent process on those subjects meeting the eligibility criteria. The informed consent process involves the following: giving a subject adequate information concerning the study, providing adequate opportunity (time) for the subject to consider all available options, responding to the subject's questions, ensuring that the subject has comprehended this information and finally, obtaining the subject's consent to participate in this study. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the subject to participate, and does not waive or appear to waive the subject's legal rights. The ICF is presented in native, non-technical language that is understandable to the subject. The ICF ensures important new information is provided to new and existing subjects throughout the clinical investigation. The Investigator or designee shall confirm the subject understands each of the following points of the study:

- The purpose of the study;
- The potential risks or adverse events that are posed by their treatment;
- Possibility of failure and the need for subsequent treatment(s);
- Alternative procedures/treatments available to the subject;
- Requirements of the study including any required rehabilitation, the need to return for the endocardial catheter ablation procedure performed by the electrophysiologist at Day 91-121 and subsequent follow-up requirements; and
- The subject's rights as a participant in the clinical study.

The Informed Consent process is finalized by completion of the ICF. Following the explanation of the study intent, the Investigator or designee shall offer to answer any of the subject's questions. If the subject then agrees to participate, his or her willingness must be documented via signatures of the ICF.

This document must be signed and dated by the subject prior to any study related procedures or enrollment (signing of informed consent). No dates should be pre-populated or completed by

someone other than the person providing the signature.

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This is a prospective, multi-center, single arm, pivotal study sponsored by AtriCure, Inc. This study will be conducted in the US and outside the US, under a single protocol approved by an IRB/EC for each site prior to implementation at the study site. The Principal Investigators (PIs) bear the responsibilities described in the Protocol Signature Page.

This clinical investigation will be conducted in accordance with this Protocol / 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. The investigator(s) will create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits, as well as maintain documentation of the type and location of these source documents.

The investigator(s) will also determine the cause and implement appropriate corrective and preventative actions to address significant noncompliance.

Up to 35 Sites (30 US and 5 OUS) will participate and up to 220 subjects will be treated as part of the study. A maximum of 40 subjects will be treated per site. Treated subjects will be assessed for primary safety through 30 days post the Epicardial Surgical Ablation Procedure and for primary effectiveness at 12 months post the Endocardial EP Ablation Procedure. All treated subjects who complete both epicardial and endocardial procedures will be followed for 5 years post the DEEP study procedure.

An independent ECG core laboratory will be utilized for assessment of continuous ECG monitoring recordings. All ECG monitoring shall be performed in accordance with the core laboratory's recommended protocol which is provided to the sites in the Study Reference Manual.

The local institutional laboratories will be utilized for analysis of serum samples obtained by the study site personnel. The laboratories will have Clinical Laboratory Improvement Amendments (CLIA) certification and College of American Pathologists (CAP) accreditation.

A quality-of-life measurement for each study subject will be obtained pre- and post-procedure using a commercially available questionnaire (The AF Effect on Quality/AFETQ, St. Jude Medical Inc., St. Paul, MN).

An Electronic Data Capture (EDC) system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common electronic case report forms (eCRFs). This system is a web-based, secure electronic software application (Clindex®) developed and maintained by Fortress Medical Systems in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements.

Serious Adverse Events (SAE) and product quality problems (for products used during the procedure), including potential and actual product use errors suspected to be associated with the use of a Food and Drug Administration (FDA) regulated drug, biologic, medical device or dietary supplement used during the course of this study will be reported by the PI to applicable authorities

including the: 1) Sponsor (AtriCure); 2) IRB/EC; 3) respective manufacturer(s); and/or 4) FDA via MedWatch Online Voluntary Reporting Process or Medical Device Reporting as appropriate.

1.0 INTRODUCTION

The objective of this study is to establish the safety and effectiveness of a **D**ual **E**picardial and **E**ndocardial ablation **P**rocedure **(DEEP)** for patients presenting with Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation utilizing the AtriCure Bipolar System and AtriCure Left Atrial Appendage (LAA) Clip in an endoscopic or open ablation procedure, followed by an endocardial mapping and ablation procedure utilizing commercially available RF based, irrigated, power controlled ablation catheters for endocardial lesions. The endocardial procedure will be staged to occur after 90 days post epicardial surgical procedure.

The data collected in this clinical study will be used to support a PMA submission to the FDA for the AtriCure Bipolar System.

Background on Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia encountered 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.[2] The Heart Rhythm Society (HRS) defines atrial fibrillation as a supraventricular arrhythmia that is characterized by chaotic and uncoordinated contraction of the atrium. It is understood by HRS, that AF consists of atrial "triggers" that induce AF episodes and an anatomic substrate that is capable of perpetuating the AF. AF leads to thromboembolism and stroke in approximately 5-10% of high-risk patients and the risk increases with age[2]. Because there are no effective atrial contractions during AF, blood stasis occurs in the atria (particularly in the appendages) and thrombi sometimes form. The American Heart Association estimates that in the United States, AF is responsible for over 70,000 strokes each year and accounts for 1.4 million outpatient visits and 227,000 hospitalizations per year.[3,4]

Atrial Fibrillation Classification

Atrial Fibrillation is also known to be a progressive disease which can potentially be controlled with medication in its most benign state but can progress to be intractable. In an effort to bring uniformity to the various degrees that AF can present, the Heart Rhythm Society (HRS) 2012 AF expert consensus statement has recommended the following AF classification scheme based upon the patterns of duration and mode of termination:

Paroxysmal: Recurrent AF (≥2 episodes) that terminates spontaneously within seven days. Episodes of AF of < 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.

Persistent: Continuous AF, which is sustained beyond seven days, or lasting greater than 48 hours and less than seven days but necessitating pharmacologic or electrical cardioversion.

Longstanding Persistent: Continuous AF of greater than 12 months' duration.

Permanent: Patients with AF in whom a decision has been made not to pursue restoration of sinus rhythm by any means.[1]

This classification system has been recognized by FDA as part of their guidance documents regarding treatment of patients with AF.

Atrial Fibrillation Treatment

Atrial Fibrillation is treated either by anti-arrhythmic drugs (AADs) or by mechanical intervention, which includes catheter ablation and/or surgical ablation. Traditionally, patients who present with symptomatic early onset AF are first prescribed AADs. Patients who are symptomatic and refractory to AADs become potential candidates for interventional procedures.

The 2012 HRS AF consensus statement recommends minimally invasive sole-therapy surgical ablation for patients who prefer a surgical approach, when catheter ablation is contraindicated, or when catheter ablation has failed one or more times.[1] This proposed IDE clinical study is focused on treating patients with Persistent or Longstanding Persistent AF who are symptomatic, have failed at least one AAD therapy, and may have received up to two (2) failed catheter ablations for the treatment of AF.

Catheter ablation techniques are designed to isolate or ablate the atrial triggers that induce AF and modify the abnormal atrial substrate that sustains AF when indicated. Since the majority of paroxysmal atrial fibrillation (PAF) is induced by pulmonary vein triggers, catheter ablation is used most commonly to isolate the pulmonary veins in patients with PAF. In the persistent forms of AF, it is essential to add other measures, such as linear lesions to modify the substrate responsible for sustaining AF. While multiple catheter ablations have proven to be successful for PAF, catheter ablation has enjoyed substantially less success when used for the persistent forms (non-paroxysmal) AF.[5, 6, 7]

The Cox-Maze III surgical technique that was pioneered by Dr. James Cox in the 1980's has excellent long-term results but remains too invasive to be widely applied in all patients with AF, especially as a stand-alone procedure. It was based on intraoperative mapping studies that documented the presence of multiple relatively large (>5cm diameter) macro-reentrant circuits in all patients during all episodes of AF. These large macro-reentrant circuits were unstable and often remained in one area for only 200 msec. However, by placing multiple lesions in the atria that were close enough together to prevent the macro-reentrant circuits from forming, the atria, by definition, could no longer fibrillate. Furthermore, by placing those lesions in the pattern of a maze, it was possible for the SA node to take over afterwards and have the resultant sinus impulse activate the entire myocardium of both atria except for the isolated pulmonary veins. The success rates of the Cox-Maze III procedure were 98% at 5 years[8], 98% at 8.5 years[9], and 94% at 15 years.[10]

The introduction of the AtriCure Bipolar System has led to the development of the Cox-Maze IV procedure, so-called because it is performed with an ablation device rather than by the "cut-and-sew" technique of the Cox-Maze III. The ultimate goal is to perform a minimally invasive endoscopic lesion set compatible with the Cox-Maze III pattern on the beating heart, without the need for cardiopulmonary bypass and with no incisions on the heart. The lesions include pulmonary vein isolation in pairs with the AtriCure Bipolar System plus roof and floor linear ablation lines that convert the pulmonary vein isolation lesions into a "box" lesion of all 4 veins and the intervening posterior left atrial wall as was done in the Cox-Maze III procedure. A "mitral line" extending from the "box lesion" down to the mitral valve annulus may be added by the catheter ablation procedure only if needed but will not be performed as part of the initial surgical procedure. The cavo-tricuspid isthmus lesion will be added during the follow-up Endocardial EP Ablation Procedure.

The Cox-Maze IV has been performed in an open chest setting on cardiopulmonary bypass with

success rates as high as 95%.[11] However, the associated complications of being on bypass are still present. With the development of endoscopic ablation instruments and the use videoscopic assisted techniques (VAT), the cardiac surgeon has the option to perform a limited maze procedure off bypass. Such minimally invasive thoracoscopic ablation limited maze procedures have produced a wide range of results (35% to 90%) depending upon the lesion set and the definition of success.[12]

Catheter ablation has been utilized to treat individuals with Persistent or Longstanding Persistent AF, however with less promising outcomes than surgery. Although frequently used to isolate triggers such as the PVs in order to treat paroxysmal AF, catheter ablation for Persistent or Longstanding Persistent AF has been less effective due to the limitations of the current catheter technology to perform reliable transmural linear lesions.[13] The results for a recent catheter ablation registry of more than 20,000 procedures reports success rates for the treatment of persistent forms of AF of less than 60%.[14] Furthermore, Kuch recently published his 5-year results with single and multiple catheter ablations for the persistent forms of AF and found that the success rate at 5 years for single catheter ablation was 20% and for multiple catheter ablations was 45%.[7]

Epicardial and Endocardial Approaches

AtriCure's Bipolar System is highly effective at creating reliable transmural ablation lines, the success rates for minimally invasive endoscopic ablation are challenged by sub-optimal mapping techniques and technologies for verification of conduction block and the inability of the surgeon to perform the valvular lesions associated with the Cox-Maze IV procedure. A minimally invasive endoscopic ablation procedure combined with conventional catheter mapping and ablation techniques and technologies enables physicians to replicate the Cox-Maze IV procedure through a minimally invasive off pump approach.

Consequently, the proposed staged epicardial and endocardial approach is being developed as an opportunity to enhance patient outcomes. Working together, the cardiac surgeon and electrophysiologist can combine their techniques and technologies to offer Persistent and Longstanding Persistent AF patients a true minimally invasive Cox-Maze IV option. During this epicardial surgical ablation and the endocardial catheter ablation approach, the endocardial catheter component of the procedure is introduced for mapping and confirmation of surgical ablation lines. The endocardial catheter can also be used for ablation to optimize a surgical lesion that may not have achieved conduction block and also to perform the cavo-tricuspid and mitral isthmus lesions which are key components of the Cox-Maze IV lesion set. This procedure is currently being performed by teams of surgeons and electrophysiologists to improve on the efficacy in the treatment of Persistent and Longstanding Persistent AF patients which currently represents a group of patients with less effective treatment alternatives.

Feasibility Clinical Investigations Conducted by AtriCure

AtriCure conducted two feasibility studies. These studies are described below:

CP2009-1: DEEP Hybrid Feasibility Study

This was AtriCure's initial feasibility IDE clinical study that examined the safety and effectiveness of a combined hybrid approach for the treatment of Persistent or Longstanding Persistent atrial fibrillation. A total of 24 subjects were enrolled and treated in this feasibility clinical study. The cardiac surgeon performed the epicardial surgical ablation immediately followed by the endocardial catheter ablation performed by an electrophysiologist. This procedure was performed

in the same procedure room.

A decision was made by AtriCure to suspend enrollment to this initial feasibility study due to the challenges for centers to perform this procedure in and proceed with a second feasibility study that have a staged approach as described below.

Subjects enrolled in this study were followed for 2 years. The primary efficacy endpoint was the absence of atrial fibrillation (AF) at the 12-month follow-up based on a 14-day auto trigger event monitor, i.e., no episodes of AF, atrial flutter, or atrial tachycardia lasting > 30 continuous seconds, while off all Class I and III antiarrhythmic therapy for at least 4 weeks (except amiodarone which must be 12 weeks), prior to assessment. The primary efficacy endpoint was achieved in 68.4% (95% CI 43.4, 87.4) of the 19 subjects with Holter data available. No episodes of atrial fibrillation or atrial flutter were detected on Holter in all 19 subjects at 12-month follow-up. The primary efficacy endpoint was not met in 6 subjects due to atrial tachycardia episodes; in 2 subjects the failure was based on the subjects being in sinus rhythm on AADs and in 4 subjects the failure was based on the subjects being noted to have AF, either on Holter or based on permanent pacemaker interrogation.

Although the sample size was small for a meaningful interpretation and the analysis was intended to be exploratory, the rate of freedom from AF (68.4%) at 12 months is consistent within the range given in the literature for this patient population.

CP2012-1: Staged DEEP Feasibility Study

AtriCure developed a second feasibility clinical study that was based on the earlier DEEP hybrid study. A staged approach was developed by AtriCure where the subject would undergo an epicardial surgical ablation performed by the cardiac surgeon and approximately 1-10 days following this procedure, the electrophysiologist would perform an endocardial ablation. This procedure occurred during the same hospitalization by the surgeon and electrophysiologist. This staged approach was believed to have logistical advantages over a combined, single-session hybrid procedure.

A total of 30 subjects were enrolled in the feasibility study, with 25 subjects treated with the surgical index procedure and 24 received the endocardial ablation procedure. The Thirty (30) Day Safety Data and annual report has been submitted to the FDA. Subjects are in follow-up and primary endpoint effectiveness data has not be evaluated as subjects are currently returning for 12-month follow up evaluations to assess freedom of AF, atrial flutter, or atrial tachycardia lasting > 30 continuous seconds.

Based on the feasibility study results, AtriCure believes that a multi-center, controlled pivotal study of a staged epicardial/endocardial approach is warranted.

Devices Used to Perform Epicardial/Endocardial Ablation

The AtriCure Bipolar System is intended to form the basis of the Cox-Maze IV lesion set with the aid of catheter-based techniques and technologies. The catheter technologies are utilized for comprehensive mapping to ensure confirmation of effective conduction block, lesion gap closure (as needed), and the creation of cavo-tricuspid isthmus lesions provided via electro-anatomic mapping and catheter-based ablation. The creation of the mitral isthmus lesion will be conducted if the subject presents in mitral isthmus dependent flutter at the time of the Endocardial EP Ablation Procedure.

This protocol shall dictate a consistent lesion set to assess the effectiveness of the use of the AtriCure Bipolar System with additional lesion creation and gap closure (as needed) and ablation provided by catheter mapping and ablation.

The devices utilized for the study include:
The AtriCure Bipolar System used in this clinical study consists of a radiofrequency (RF) generator (ASU2 RF Generator/US, ASU3 RF Generator/OUS), a switchbox console (ASB3 Switch Matrix), two single use RF clamp handpieces (EMR2 and EML2), three single use bipolar RF Pens (MAX 5, MLP1, and MCR1) and the Glidepath Tape (GPT 100). AtriClip PRO LAA Exclusion System (PRO1 or PRO2) is also used. See **Section 6.0** for a description of the devices.

Left Atrium

Ablation catheters used for endocardial lesions in the left atrium (referred to as "LA ablation catheters") should be:

- Biosense Webster Thermocool Product line (Navistar Thermocool Catheter, Biosense Webster EZ Steer Thermocool Catheter Nav, Thermocool SF Catheters, or Biosense Webster Thermocool SmartTouch) when used with the Stockert 70 RF generator and the CoolFlow Irrigation Pump.
- Abbott (St. Jude) TactiCath Quartz Catheter Product line (TactiCath Quartz Catheter, TactiCath Contact Force Ablation Catheter, Sensor Enabled) when used with the following compatible accessories:
  - RF generators
    - RF power output adjustable 10-50 Watts
    - RF output frequency 450-550KHz
    - Temperature limit adjustable 30-50 degrees Celsius
    - Thermocouple 1 Type T
    - Operating Impedance Range 50-300 Ω
  - Irrigation pumps (St. Jude Medical Cool Point Irrigation Pump or the Biosense Webster CoolFlow Irrigation Pump).

For gap closure (as needed) and creation of the mitral isthmus lesions and CFAE ablation, the RF based, irrigated, power-controlled ablation catheter shall be used in a consistent manner as outlined in the product Instructions for Use.

Right Atrium

Ablation catheters used for endocardial lesions in the right atrium (referred to as "RA ablation catheters") should be:

- RF based
- Irrigated or non-irrigated
- Power controlled or temperature controlled

Further, the procedure should incorporate electro-anatomic mapping. The electrophysiologist may also use additional commercially approved catheters for the cavo-tricuspid isthmus lesion, at the physician's discretion. The use of cryo balloon catheters will not be permitted. Electrophysiologists may use irrigated or non-irrigated RF ablation catheters, depending on the Electrophysiologist's preference.

2.0 STUDY OBJECTIVE

The objective of this study is to establish the safety and effectiveness of a dual epicardial and endocardial ablation procedure for patients presenting with Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation utilizing the AtriCure Bipolar System and AtriClip PRO LAA Exclusion System in an endoscopic or open ablation procedure, followed by an endocardial mapping and ablation procedure utilizing commercially available RF based, irrigated, power controlled ablation catheters for endocardial lesions. The endocardial procedure will be staged to occur after 90 days post epicardial surgical procedure.

The data collected in this clinical study will be used to support a PMA submission to the FDA for the AtriCure Bipolar System.

3.0 STUDY ENDPOINTS

3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).
Any arrhythmia that occurs within the blanking period or during the “AAD Optimization Period” visit will not be considered a failure (Visit 5 up to Visit 10). The rhythm status used for evaluation of this endpoint shall be derived from regularly scheduled monitoring (i.e., Holter, Zio™ Patch, or 30 second ECG), as well as any symptom driven monitoring that is performed.

The following scenarios shall constitute a failure of the primary effectiveness endpoint:

1. Any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds duration) that occurs at any time beginning at the 6-month visit and through the 12-month visit.
2. Any previously failed class I or III AAD administered at a dose higher than baseline and between the 6-month visit and the 12-month visit.
3. Any newly introduced class I or III AAD usage beginning at the 6-month visit through the 12-month visit.
4. DC cardioversion for AF, atrial flutter, or atrial tachycardia that takes place at any time beginning at the 6-month visit through the 12-month visit.
5. Catheter ablation or surgical treatment for AF, atrial flutter, atrial tachycardia that takes place at any time beginning at the 3-month visit and ending at the 12-month visit.
6. Two or more repeat catheter ablations within the 2nd blanking period
7. The use of a non-study device for creation of any lesions during the surgical epicardial ablation procedure

For the purposes of this study, atrioventricular nodal reentrant tachycardia (AVNRT), inappropriate sinus tachycardia, and Wolff–Parkinson–White syndrome (WPW) will not be considered procedure failures.

For this study, AtriCure defines failure of an antiarrhythmic drug (AAD) to include ineffectiveness or intolerance of the AAD.

3.2 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint consisting of any one or more of the following events if they are adjudicated by the CEC to be serious adverse events (SAEs) and related to device/procedures as follows:

1. The AtriCure Bipolar System and/or the AtriClip Pro LAA Exclusion System, within 30 days following the epicardial surgical ablation procedure; or
2. The epicardial surgical ablation procedure within 30 days following the epicardial procedure; or
3. The endocardial index procedure (or a repeat endocardial ablation procedure performed during the blanking period) within 7 days following an endocardial ablation procedure.

Events except as otherwise specified for a particular condition include:

a. death (regardless of cause)
b. stroke
c. transient ischemic attack (TIA)
d. myocardial infarction (MI)
e. pulmonary or systemic embolism
f. pericarditis resulting in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires a new hospitalization, or persists for more than 30 days following the ablation procedure
g. excessive bleeding, defined as one or more of the following:
    i. re-operation to control bleeding within 7 days post-epicardial surgical procedure; or surgery to control bleeding within 7 days post-endocardial ablation procedure, if related to the endocardial catheter ablation
    ii. receipt of ≥ 2 units of blood transfused in a 24-hour period during the first 7 days post-epicardial surgical procedure; or within the first 7 days post-endocardial ablation procedure, if related to the device or procedure
    iii. conversion to sternotomy or thoracotomy that requires ≥ 2 units blood to be transfused, or performed to treat hypotension, cardiac arrest, or repair of a cardiac injury.
h. wound infection at surgical site requiring re-operation for wound debridement
i. atrio-esophageal fistula (from the time of surgical procedure through 12-month follow-up visit)
j. permanent phrenic nerve paralysis, defined as paralysis that remains unresolved at the 12-month follow-up visit
k. permanent pacemaker implantation that is a direct result of injury to the specialized conduction system (SA node or AV node) during the epicardial surgical ablation procedure
l. pulmonary vein (PV) stenosis of >70%, as measured at any time after the catheter ablation procedure through the 12-month follow-up visit
m. major vascular access complications, including development of a hematoma, an arteriovenous fistula, or pseudoaneurysm that requires surgical repair or transfusion, prolong hospital stay, or require a new hospital admission

3.3 Secondary Effectiveness Endpoints

1. Exclusion of the LAA, defined as defined by lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA. This

endpoint will be measured at the 12-Month (Visit 11) (approximately 15 months post AtriClip placement). The AtriClip effectiveness population will be utilized for analysis of this endpoint.
2. Exclusion of the LAA, defined as lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA. The endpoint will be measured intra-procedurally (Visit 2), and at the Endocardial EP Ablation Procedure (Visit 5). The AtriClip effectiveness population will be utilized for analysis of this endpoint.
3. Acute procedural success of epicardial surgical procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins, as well as the "box."
4. Acute procedural success of endocardial catheter procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins and the "box", as well as bi-directional block of the cavo-tricuspid isthmus.
5. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter without AAD, defined as no documented event >30 seconds in duration (or for the entire length of an ECG tracing) with no utilization of AADs beyond the blanking and AAD optimization periods, except as previously failed without an increase in dose. This endpoint will be measured through the 12-month, 2-, 3-, 4-, and 5-year visits (Visits 11-15) via continuous 24-hour ECG monitor.
6. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter regardless of AAD, defined as no documented event >30 seconds in duration (or for the entire length of a 30 second ECG tracing) regardless of AAD usage. This endpoint will be measured through the 12-month, 2-, 3-, 4-, and 5-year visits (Visits 11-15 via cumulative 24-hour ECG monitoring).
7. Freedom from any documented Atrial Fibrillation, atrial flutter, or atrial tachycardia lasting >10 minutes in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).
8. Change in Quality of Life, defined as the total AFEQT score measured at the 12-month follow-up visit minus the score at the baseline visit. The score will be calculated per the AFEQT scoring manual.

3.4 Secondary Safety Endpoints

All secondary safety endpoints are supplemental and intended to provide a more complete safety profile for the DEEP procedure. These endpoints will not be tested for labeling purposes.
1. Major surgical events – This will be a composite safety endpoint within 30 days of the epicardial surgical procedure, as otherwise defined in the primary safety endpoint.
2. Major catheter events – This will be a composite safety endpoint within 7 days of the endocardial catheter procedure, as otherwise defined in the primary safety endpoint.
3. 30-day surgical SAEs - This will include all SAEs that occur within 30 days of the epicardial surgical procedure and that are adjudicated to be related to the device or to the procedure.
4. 12-month DEEP SAEs - This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure.
5. Unresolved SAEs – This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure and that are not fully resolved by the 12 months visit. These events shall include any procedure-related deaths, strokes with residual disability, unresolved phrenic nerve damage, or other such events that are adjudicated to have resulted in chronic disability or permanent damage.
6. Any serious adverse event through the 12-month follow-up visit, regardless of attribution.
7. Incidence of stroke or TIA at 12, 24, 36, 48, 60-month visits.
8. Any esophageal injury that meets all of the following criteria: identified post epicardial ablation, adjudicated by core lab to be a thermal injury with perforation, and related to an AtriCure ablation device, through 30-days post epicardial procedure.

3.5 Secondary Endpoints – Health Economics

All health economics endpoints are exploratory in nature.

1. Utilization of cardioversion, defined as the number of cardioversion events (visits) that a subject had in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.
2. Hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the number of readmissions in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.
3. Total length of stay for all hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the sum of the length of stay for each such visit within the last 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11-15) follow-up visits.
4. Emergency Room Visits for AF, atrial flutter, or atrial tachycardia, defined as the number of visits in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.

3.6 Blanking Periods

It is traditional to have a "blanking period" following any intervention for cardiac arrhythmias. During the blanking period, neither a recurrence of the pre-interventional arrhythmia that was treated nor a new arrhythmia resulting from the intervention itself is considered to represent a "failure" of the interventional procedure. The traditional blanking period for the interventional treatment of atrial fibrillation has been 90 days.

There are two reasons for suggesting that each blanking period last for approximately 90 days following the specific intervention:

- To allow the surgical lesions and later the catheter ablation lesions to fully heal; and
- To allow the electrophysiological characteristics of the atrium, such as local refractory periods, conduction velocity, etc., to return to their pre-intervention baselines. Even in patients who have a cut-and-sew Maze procedure for atrial fibrillation, in which "healing" of the lesions is not an issue, the blanking period is still 90 days because of the need to allow the atrium to heal completely from the surgery.

Since the proposed DEEP procedure requires two individual interventional procedures, two separate blanking periods are included in this protocol. The 1st blanking period is from the time of the Epicardial Surgical Ablation Procedure through the Endocardial EP Ablation Procedure (which is approximately 90 days). The 2nd blanking period is 90 days post Endocardial EP Ablation Procedure. During these intervals, the effectiveness of the Epicardial/Endocardial Ablation Procedure is not evaluated for arrhythmia recurrence and re-intervention to address atrial dysrhythmia may be performed.

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study and Design – Description

Study Design and Timeline				
Epicardial Surgical Ablation Procedure	**1st Blanking Period**	**Endocardial EP Ablation Procedure**	**2nd Blanking Period**	**Subject Follow-Up Period**
Day 1	**Epicardial Surgical Ablation Procedure through Endocardial EP Ablation Procedure**	**Day 91 (+ 30 days)**	**90 Days Post Endocardial EP Ablation Procedure**	**5 years post Endocardial EP Ablation Procedure**

This study consists of a baseline period (up to 45 days in length), followed by the Epicardial Surgical Ablation Procedure followed by the 1st Blanking Period, the Endocardial EP Ablation Procedure followed by a 2nd Blanking Period and 5-year subject follow-up. Phone contact with the subjects will be attempted at 18, 30, 42, and 54 months.

The overall plan for all subjects consists of the following elements:

- Subjects will be informed about the nature of the research, given the ICF to read, and if the subject understands and agrees to the procedure will be asked to provide written informed consent;
- Subjects will undergo baseline procedures to determine if inclusion and exclusion criteria are satisfied and the subject is eligible for the study procedure;
- Subjects will undergo the DEEP procedure, per protocol;
- Subjects will be followed for up to 5 years to evaluate outcomes and potential complications;
- Subjects will be assessed for AEs and will be instructed to notify the PI of any AEs that occur during the entire course of the study. Data will be recorded into subject source medical records.

4.2 Selection of Study Population

4.2.1 Recruitment

A Screening Form will be completed for all patients who meet the inclusion criteria. Patients will be provided the IRB/EC approved ICF and will have the opportunity to read, understand, and have their questions answered prior to signing the ICF. If the patient agrees to participate in the study and signs consent, the ICF will be completed. The subject must sign and date the ICF prior to any study-specific procedures being performed. The person reviewing the ICF with the subject will also sign and date the ICF. The subject will be given a copy of the signed ICF to keep.

This clinical investigation will enroll male and female subjects from the general population. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

Upon entering subject enrollment information into Clindex, each subject will be assigned a unique ID number sequentially in ascending order. All subjects who sign the ICF will be documented in a Screening and Enrollment Log.

4.2.2 Enrollment

Patients are considered **enrolled** in the study when they have signed an informed consent. Subjects are considered **treated** upon induction of anesthesia during the Epicardial Surgical Ablation Procedure.

4.2.3 Inclusion Criteria

Subjects satisfying the following inclusion criteria will be considered the screening population and will be eligible for participation in this study:

1. Patient is willing and able to provide written informed consent.
2. Patient is ≥18 years of age and ≤ 75 years of age at time of consent.
3. Patient has symptomatic (e.g., palpitations, shortness of breath, fatigue) Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation refractory to a minimum of one Class I or Class III AADs.

   Persistent AF: is defined as continuous AF lasting beyond seven days but no more than one year, or lasting greater than 48 hours and less than seven days but necessitating pharmacologic or electrical cardioversion.

   Longstanding Persistent AF: is defined as continuous AF of greater than 12 months duration.

   Note: Persistent or Longstanding Persistent AF must be documented as follows:

   Persistent AF:

   - Physician's note indicating continuous AF ≥ 7 days but no more than one year, or AF lasting > 48 hours and < 7 days but necessitating pharmacologic or electrical cardioversion; AND
   - Two (2) electrocardiograms from any form of rhythm monitoring (e.g., 12-lead ECG, Holter, event monitor, Implantable Loop Recorder (ILR), pacemaker etc.) documenting continuous AF, with electrocardiograms taken at least 7 days apart, for subjects with sustained AF ≥7 days.

   Longstanding Persistent AF:

   - Physician's note indicating continuous AF > one year; AND
   - 24-hour Holter or other form of continuous rhythm monitoring (e.g., event monitor, Implantable Loop Recorder (ILR), pacemaker etc.) obtained within 90 days prior to the surgical ablation procedure showing continuous AF.

   Note: 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 longstanding persistent.)
4. **Patient may have had up to two (2) previously failed catheter ablations to** treat atrial fibrillation using catheter ablation are eligible, if they present with symptomatic Persistent or Longstanding Persistent AF. Previous catheter ablation must have occurred greater than three (3) months prior to informed consent.
5. Patient is willing and able to receive all of the study related procedures and attend the

scheduled follow-up visits.

4.2.4 Exclusion Criteria

Subjects will be excluded from the study for any of the following:

1. Patient has a documented history of **continued** AF >10 years.
2. Patient has refractory hypertension, defined as systolic (>150 mm Hg) or diastolic (> 90 mm Hg) blood pressure that remains uncontrolled despite sustained therapy.
3. Patient has a documented history of pulmonary hypertension (Class III or IV with a mean pulmonary artery pressure >40 mm Hg).
4. Patient exhibits pulmonary vein stenosis in one or more of the pulmonary veins >50 % stenosis.
5. Patient has had an EP catheter ablation procedure to treat atrial fibrillation within 3 months prior to signing consent.
6. Patient is pregnant or lactating or plans on becoming pregnant within the next 2 years.
7. Patient has a medical condition with less than 5 years life expectancy.
8. Patient has undergone prior cardiothoracic surgery (lungs or mediastinum).
9. Patient had previous thorax trauma, which resulted in a pneumothorax or hemothorax.
10. Patient has sleep apnea and is non-compliant to current regimen of treatment, i.e., CPAP.
11. Patient is on home oxygen therapy or has moderate to severe Chronic Obstructive Pulmonary Disease (COPD) (FEV1/FVC < 70% predicted) or patient is considered intolerant to single lung ventilation.
12. Patient has NYHA Class IV heart failure.
13. Patient has an uncorrected, reversible cause(s) of atrial fibrillation (e.g., hyperthyroidism, electrolyte imbalance).
14. Patient is currently being treated for arrhythmias other than atrial fibrillation (AF) or atrial flutter.
15. Patient has documented history of previous catheter ablation with perforation.
16. Patient has documented history of pericarditis, tamponade, or clinically significant pericardial effusion.
17. Patient has evidence of underlying structural heart disease requiring surgical treatment (i.e., valve disease requiring repair or replacement within 12 months following surgical ablation procedure).
18. Patient has evidence of underlying CAD requiring intervention (either surgical, i.e., CABG, or catheter).
19. Patient has an ejection fraction < 30% (based on baseline transthoracic echocardiography or equivalent diagnostic test).
20. Patient has a measured left atrial diameter >5.5 cm in parasternal long axis view (based on baseline transthoracic echocardiography or equivalent diagnostic tests).
21. Patient suspected to have renal insufficiency based on elevated creatinine and BUN (urea) levels.
22. Patient on renal dialysis.
23. Patient has significant liver disease (e.g., cirrhosis) as evidenced by the following liver function tests: total bilirubin > 2x ULN, in association with AST/ALT (or SGOT/SGPT) > 3x ULN. *Note: if the required liver function test results do not exceed specified limits, and the investigator's level of suspicion remains high for significant liver disease, if other clinical evidence of significant liver disease (e.g., documented esophageal varices, hepatic encephalopathy) is present and/or imaging study results consistent with significant liver disease are available, this information should be utilized for exclusion.*

24. Patient had a stroke/cerebrovascular accident (CVA) within previous six months prior to signing informed consent.
25. Patient has known carotid artery stenosis greater than 80%.
26. Patient has evidence of significant active infection or endocarditis.
27. Patient is unable or unwilling to undergo TEE.
28. Patient's BMI is >40. The medical history of patients with a BMI between 36 and 40 must be reviewed by the study Principal Investigators prior to treatment of the patient to ensure patient meets acceptable health criteria for the epicardial and endocardial ablation procedures.
29. Patient has presence of thrombus in the left atrium, or the left atrial appendage determined by echocardiography (either at baseline TTE (or equivalent diagnostic test) or intraoperative TEE).
30. Patient has history of blood dyscrasia or clotting disorder (i.e., Idiopathic Thrombocytopenic Purpura [ITP] or Thrombotic Thrombocytopenic Purpura [TTP]).
31. Patient has contraindication to anticoagulation that in the opinion of the investigator poses undue risk to the patient from participating in the endocardial EP procedure.
32. Patient has a documented thromboembolism within the previous six months prior to signing informed consent.
33. Patient has an atrial myxoma.
34. Patient has a mural thrombus or mural tumor.
35. Patient has a condition or congenital anomaly which prevents required surgical or catheter access.
36. Patient has co-morbid condition that, in the opinion of the investigator, poses undue risk of general anesthesia or port access cardiac surgery.
37. Patient is currently abusing drugs or alcohol.
38. Patient is currently or has participated in a clinical study in the last 3 months prior to signing informed consent. Participation in survey clinical studies with no treatment is not an exclusion criterion.
39. Patient has a psychological disorder that could interfere with provision of informed consent, completion of tests, therapy, or follow-up.
40. Patient has a condition that, in the opinion of the investigator, may jeopardize the patient's well-being and/or the soundness of this clinical study.
41. Patient has a pre-existing esophageal condition that required (or requires) endoscopic therapy or surgical treatment.

4.3 Removal of Subjects from Study

In accordance with the current revision of the Declaration of Helsinki and the Code of Federal Regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw; all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. Subjects who withdraw from the study will not be replaced.

The primary reason for early termination and the date of termination will be recorded in the electronic case report form. Reasons may include:

Investigator Decision

If the subject experiences an adverse event and the Principal Investigator or Medical Monitor believes it is in their best interest to discontinue participation in the study, the subject will be

withdrawn from the study.

Lost to follow-up
When contact with the subject has been lost without completing the final visit assessment, and every attempt to contact has failed, the subject will be considered lost to follow-up. Final documentation regarding all attempts to contact the subject requesting their return for the **final visit (Visit 15**) should be documented.

Enrolled but Not Treated
Subject signed the ICF but did not undergo the Epicardial Surgical Ablation Procedure because they did not meet inclusion exclusion criteria or because the subject withdrew consent prior to anesthesia.

Withdrawal of consent after treatment
The subject withdraws consent for participation in the study. Any method of contact with the subject in which they state they no longer want to participate in the study specific activities constitutes withdrawal of consent. When possible the reason for withdrawal will be documented.

Death
Subject expires after enrollment into the study.

Site Termination or Study Termination
A site or study may be terminated. When this occurs all subjects at the site will be withdrawn and documented as early termination. Reasons for site or study termination may include, but are not limited to the following:

- Administrative Concerns (e.g., inadequate subject enrollment, Investigator/institution non-compliance, change of business strategy, etc.);
- Safety Issues, including those due to non-compliance, which substantially affect the risk to benefit ratio of the study subjects at a site or for the study as a whole;
- Regulatory Body Mandate(s)

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:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects;
- The Data Safety Monitoring Board (DSMB) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects);
- Further product development is cancelled.

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 (including devices) 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 the **DATA MANAGEMENT AND INTEGRITY** section of this CIP / Protocol.

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 Study 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.

Other (which may include):

- Protocol deviation, noncompliance or violation
- Sponsor recommendation
- Device/procedure failure

4.4 Follow-up for Early Terminated Subjects

Given the nature of the study procedures, there are situations where subjects may terminate from the study early that are not described above. The required subject follow-up, depending on the study procedures completed, is as follows:

- If an enrolled subject is found to not meet the study eligibility criteria, or withdraws consent before the induction of anesthesia, the subject will exit the study (complete study exit page) without study follow-up.
- If a subject is enrolled and undergoes anesthesia (treated) (e.g., clot is detected in LA or LAA), the subject will complete a limited discharge study visit and the 30-day assessment and then will exit the study (complete study exit page). The procedures required for the limited discharge and 30-day Visit are:
  - Targeted Physical Examination
  - Medication Review
  - Adverse Event Assessment
  - Discharge Date (for hospital discharge only)

If a subject is enrolled and is treated and is **converted to a sternotomy or thoracotomy** during the Epicardial Surgical Ablation Procedure, the subject will be followed through the 12 Month visit. After the 12-month follow up visit, the subject will exit the study (complete study exit page) without additional study follow-up.

If a subject is treated with the Epicardial Surgical Ablation Procedure, and withdraws before the Endocardial Ablation Procedure, the subject will be followed for at least to the 1-Month Visit after the Epicardial Procedure to follow for safety. After the 1-Month follow up visit, the subject will exit the study (complete study exit page) without additional study follow-up.

5.0 DUAL EPICARDIAL AND ENDOCARDIAL PROCEDURE

5.1 Epicardial Surgical Ablation Procedure

5.1.1 General Description

Note: A recommended surgical technique is presented below. It is recognized that individual patient anatomic variation, surgical conditions, or surgeon preference may necessitate modifications to the outlined procedures. ***Regardless, surgeons must adhere to all AtriCure devices instructions for use (IFU).***

The Epicardial Surgical Ablation Procedure is performed in an operating room with readily accessible emergency equipment and resources including cardiopulmonary bypass capabilities, adequate blood products, external and internal defibrillator pad/paddles, proper anesthesia administration, and monitoring capabilities.

The goal of the Epicardial Surgical Ablation Procedure is to produce a set of lesions that are based upon the standard Cox-Maze IV lesion set without requiring the surgeon to perform either the left atrial "mitral line" or the right atrial "flutter line" (CTI), both of which are difficult or impossible to perform from outside the heart. Ganglionated Plexi (GP) shall also be tested and ablated as appropriate.
It is recommended that the left atrial appendage be excluded in all subjects if the anatomy will accommodate the procedure with the AtriClip PRO.

Measures to Identify and Protect the Esophagus and Phrenic Nerve Structures during the Epicardial Surgical Ablation Procedure

To decrease the risk of Atrio-Esophageal Fistula (AEF) occurrences, please use the following techniques whenever the MLP1 or MCR1 are used to ablate:

- Determine the location of the esophagus utilizing thoracoscopic visualization and the TEE probe.
- Prior to energy delivery, the Transesophageal echocardiography (TEE) probe should be retracted from the area of ablation as a measure to protect the esophagus and other surrounding tissue structures.
- **Ablation**: Ablations should be visualized, and atrial tissue should be elevated up and away from the posterior pericardium with the ablation device(s) in order to avoid collateral injury to surrounding tissue.
- **Post Ablation:** Prior to repositioning the device and prior to resting the atrium onto the posterior pericardium, the device should remain in place for 30 seconds while simultaneously quenching the device, the ablated tissue, and the surrounding tissues with saline. This will allow these areas to adequately cool.
- In addition, it is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure. [Proton Pump Inhibitors (PPIs) are recommended, however; if the patient cannot tolerate PPIs, an H2 receptor antagonist or other acid reducing agent can be prescribed.]
- Esophageal temperature monitoring will not be used during the epicardial procedure.

To decrease the risk of phrenic nerve injury, please use surgical techniques to identify and retract the phrenic nerve (see Section 5.1.5).

Note: The epicardial procedure may be recorded to electronic media for visualization (i.e., thumb drive, DVD, external hard drive). Electronic recording media will be labeled and submitted to the Sponsor as requested.

5.1.2 Lesion Set - General Description

The lesion set for the epicardial surgical ablation procedure will be primarily based upon the Cox-Maze IV lesion set. These lesions will consist of bi-lateral pulmonary vein isolation, roof and floor connecting lesions, and a lesion from the left superior pulmonary vein isolation to the base of the left atrial appendage. These lesions are shown in **Figure 1a and Figure 1b**.

The EP will make the cavo-tricuspid isthmus line during the Endocardial EP Ablation Procedure, extending the lesion from the tricuspid annulus to the orifice of the Inferior Vena Cava shown in **Figure 2**.

The Ligament of Marshall may be dissected by the surgeon to mobilize the left pulmonary veins (and for any potential antiarrhythmic effects) for optional placement of ablation clamps. Ganglionated plexi (GP) testing and ablation are required on both the left and right sides.

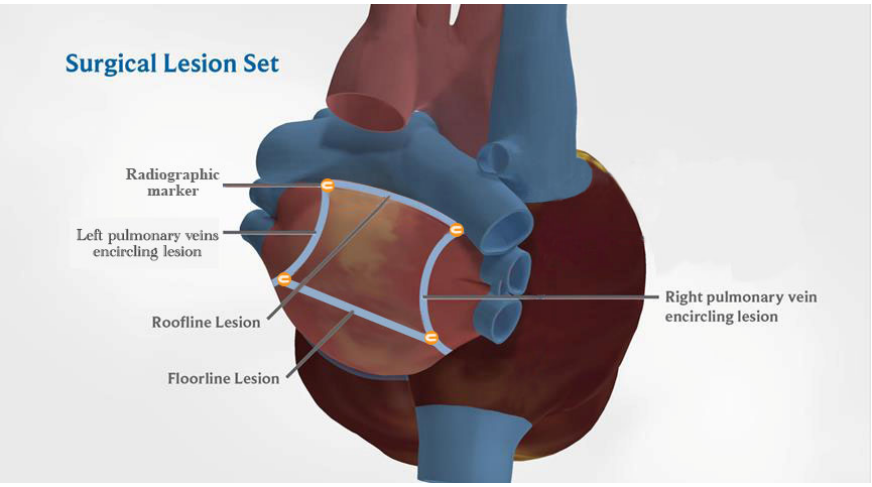


Figure 1a: Epicardial Lesion Set

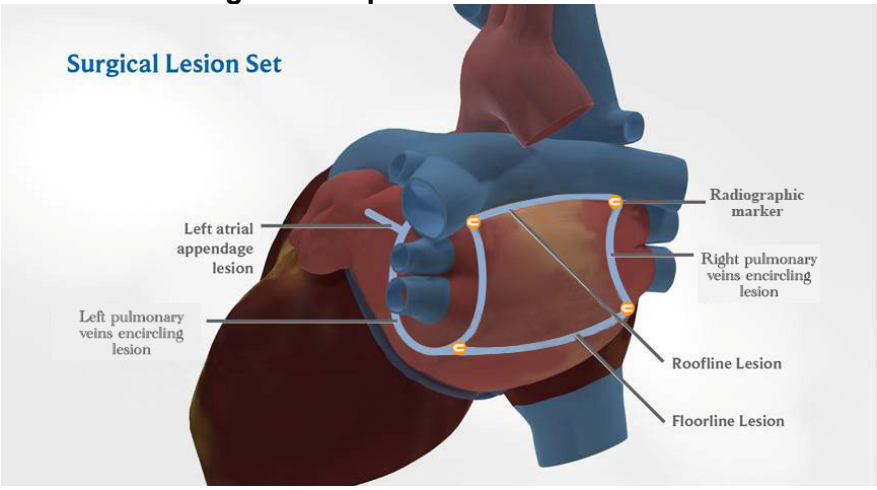


Figure 1b: Epicardial Lesion Set

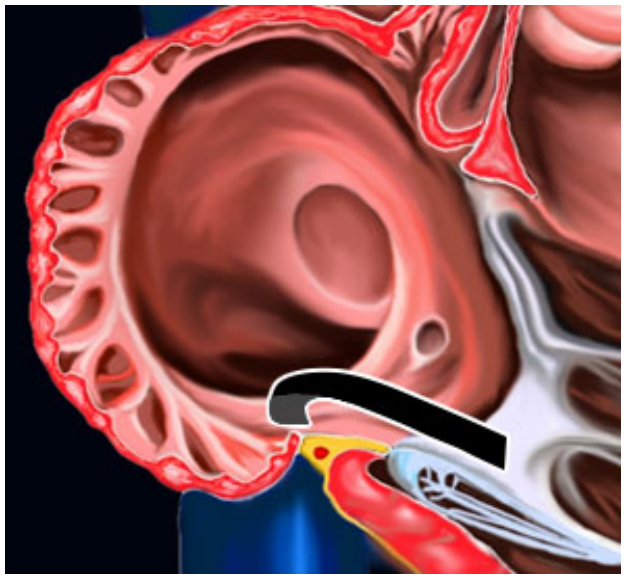


Figure 2: Cavo-tricuspid isthmus line endocardially, extending the lesion from the tricuspid annulus to the Eustachian Ridge

5.1.3 Epicardial Surgical Ablation Procedure-Overview

The checklist of epicardial surgical based lesions, highlighting the required lesions is summarized below.

Right Sided Approach

Pulmonary vein isolation and connecting linear lesions will be performed utilizing a minimally invasive endoscopic approach. After induction of general anesthesia and use of a dual-lumen endotracheal tube to provide unilateral ventilation, the following will be performed:

- Dissection using the Wolf Lumitip Dissector (MID1) and the Glidepath Tape (GPT100)

- Right Side GP Testing and Ablation (MAX5, MLP1 and/or MCR1);
- Right Antral Pulmonary Vein Isolation (EMR2) and testing (MAX5);
- Start Right sided Roof (or "Dome") Line through Transverse Sinus using Coolrail Linear Pen (MCR1) and/or the Isolator Linear Pen (MLP1) (approximately half of the line to be completed from the right side);
- Start Right sided Floor (or "Inferior") Line using Coolrail Linear Pen (MCR1) and/or the Isolator Linear Pen (MLP1) (approximately half of the line to be completed from the right side);
- Place radio-opaque vascular clips on the epicardium at the junction of the roof and floor lines and the right and left pulmonary vein isolations (LPV & RPV) to assist the Endocardial EP Ablation Procedure (see Figures 1a &1b).

Left Sided Approach

- Wolf Lumitip Dissector (MID1) and the Glidepath Tape (GPT100);
- Left Side GP Testing and Ablation (MAX5, MLP1 and/or MCR1);
- Obliterate Ligament of Marshall;
- Left Antral Pulmonary Vein Isolation (EMR2) and testing (MAX5);
- Finish ablation of the Roof (or "Dome") Line using the MCR1 and/or MLP1;
- Finish ablation of the Floor (or "Inferior") Line using the MCR1 and/or the MLP1;
- LSPV to left atrial appendage using the MAX5, and/or MCR1 and/or the MLP1;
- Exclude the LAA using the AtriClip PRO.

5.1.4 Epicardial Surgical Ablation Procedure

Pre-Operative Antithrombotic Therapy

To protect subjects from bleeding or a thromboembolic event, a **recommended** process for antithrombotic therapy is provided as outlined below. Investigators may utilize their institutional procedures for anticoagulation/antiplatelet therapy, in recognition of various oral anticoagulants available as well as individual subject factors such as $CHADS_2$ or $CHA_2DS_2VAS_c$ score.

Pre-Procedure

Subjects who are taking warfarin or a novel oral anticoagulation (NOAC) therapy should have their anticoagulation managed in accordance with the Institution's best practice protocols during the peri-operative period. Bridging anticoagulation during the 24 to 48 hours after stopping NOACs and prior to the intervention should be consistent with the institution's standard of care.

Pre-Operative Proton-Pump Inhibitor (PPI) Therapy

It is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure.

Patient Education

Patient will be counseled regarding AEF warning signs and treatment. The following will be provided to the patient:

- Patient Educational Brochure
- Patient Emergency Wallet Card

Subject Preparation in Procedure Room

The subject is prepped and draped so the surgeon has access to the entire lateral thorax bilaterally, the sternum, and both groin areas in case they should be needed for urgent access.

- Non-sterile external defibrillator pads are placed behind the right shoulder and on the left flank, away from port sites. Alternatively, if sterile external defibrillator pads are available, one can be placed over the sternum and one directly posterior on the back of the subject.

General anesthesia is induced, and the subject is intubated using a dual-lumen endotracheal tube, in order to allow unilateral (single-lung) ventilation. ***If the placement of the dual-lumen endotracheal tube (single lung isolation) is not achieved, the subject shall not have the study procedure performed.***

Esophagoscopy
An esophagoscopy must be performed prior to placement of access ports for the epicardial surgical intervention. The purpose of the esophagoscopy is to gather a baseline assessment of the esophagus.

Transesophageal Echocardiography
Transesophageal echocardiography (TEE) must be performed prior to any epicardial surgical intervention. The purpose of TEE is to assess for presence of thrombus. ***If a thrombus is present in the left atrium on TEE, the subject shall not have the study procedure performed.***

If the subject continues to meet all study eligibility criteria, the following steps are performed:

Note: The transesophageal echocardiography probe should be retracted from the area of ablation prior to energy delivery as a measure to protect the esophagus and other surrounding tissue/structures.

5.1.5 Epicardial Surgical Ablation - Detailed Technique

AtriCure Device Energy Delivery Parameters
The following AtriCure devices may be used for this surgical ablation procedure and are described below in **Section 6.0**:

a. EMR2/EML2 Clamp
b. Isolator Long Pen TT (MAX5)
c. Coolrail Linear Pen (MCR1)
d. Isolator Linear Pen (MLP1)
e. RF Generator Model (ASU2/ASU3)
f. Switch Matrix (ASB3)
g. Glidepath Tape (GPT100) (accessory device)
h. Wolf Lumitip dissector (MID1) (accessory device)
i. AtriClip PRO LAA Exclusion System (PRO1 or PRO2)
j. Gillinov Cosgrove Selection Guide (CGG1) (accessory device)

EMR2/EML2 Clamp
When using the AtriCure devices for ablation, the time necessary to create a transmural lesion depends on tissue thickness, composition, and the length of tissue captured between the electrodes. The following table describes the average expected time (seconds) and energy delivery (joules) for respective tissue thickness. Values are expressed per unit volume of tissue

captured between the electrodes. These data were obtained during ablations on ex vivo (excised bovine) tissues and will generally be lower for in vivo (live human) tissues.

Tissue Thickness	Time to Transmurality per Unit Volume (sec/mm^3)		Energy Delivered per Unit Volume (J/mm^3)	
2 mm	0.049	0.007	0.76	0.11
5 mm	0.033	0.006	0.57	0.10
10 mm	0.032	0.009	0.55	0.16

Isolator Long Pen TT (MAX5)

Stamping ablation technique: Apply constant firm pressure to the tissue without movement. Maintain full contact of the electrode surface with the tissue. A stamping lesion is approximately 8 mm x 6 mm. If creating longer linear lesions with the Stamp technique, overlap the contiguous ablations by 50% to ensure a continuous and complete lesion.

Stamping Lesion Depth*

Duration (seconds)	10	15
Lesion Depth (mm)	3.3 – 3.8	3.8 – 4.4

* Data was obtained from ablations performed on excised bovine myocardium and represent 95% confidence intervals. Results may vary based on live tissue properties.

Coolrail Linear Pen (MCR1)

The depth of the lesion will be determined by the duration of activation. If creating connecting linear lesions, overlap the contiguous ablations at most 50% to ensure a continuous and complete lesion.

Cardiac Tissue Lesion Depth (mm)*

Duration (seconds)	20	30	40
Tissue Thickness (mm)	4.1 – 4.5	4.8 – 5.2	5.1 – 5.4

* Data was obtained from ablations performed on excised bovine myocardium and represent 95% confidence intervals. Results may vary based on live tissue properties.

Isolator Linear Pen (MLP1)

Apply constant firm pressure to the tissue without movement. Maintain full contact of the electrode surface with the tissue. A lesion is approximately 20 mm x 8 mm.

If creating connecting linear lesions, overlap the contiguous ablations at most 50% to ensure a continuous and complete lesion.

Lesion Depth*

Ablation Time (seconds)	20	30	40	Repeat 40s ablation
Lesion Depth (mm)	4.5 – 4.9	5.1 – 5.5	5.7 – 6.0	6.6 – 6.9

* Data was obtained from ablations performed on excised bovine myocardium and represent 95% confidence intervals. Results may vary based on live tissue properties.

Refer to the appropriate device Instructions for Use for further details.

Right Side Endoscopic Port Placement

This phase of the operation is typically performed with three to four ports. Starting on the subject's right side, a 5mm or 10mm diameter port is introduced in the mid-axillary line in the area of the third or fourth intercostal space. Endoscopic visualization is helpful in safely inserting this initial port. CO2 insufflation is performed to expand the field and depress the diaphragm. A 0- or 30-degree scope is recommended to obtain good visualization throughout the thorax, once absorptive atelectasis of the lung has taken place.

The other ports (5mm or 10mm diameter) are placed on the subject's right side. One port is placed in the mid-clavicular line in approximately the second intercostal space, and the other port in the mid-axillary line in approximately the 6th or 7th intercostal space. Each of these ports are placed so that instruments passed through them can access the transverse sinus, behind the superior vena cava and immediately cephalad to the right atrial appendage as well as the oblique sinus. At the discretion of the surgeon, a fourth port may be placed to aid exposure or retraction.

Right-Side Pericardium & Associated Great Vessel Exposure

Working through these port sites, the right pericardium is opened from the diaphragm to the level of the aorta, approximately 2 cm anterior to the phrenic nerve. ***Great care must be taken at all times to not injure the phrenic nerve.*** Pericardial retraction sutures may be placed and brought out through the posterolateral chest wall (ensure that these retraction sutures do not stretch the phrenic nerve).

Access to the floor of the left atrium is now obtained to create the exposure necessary to construct the inferior connecting lesion that will join the two pulmonary vein isolations along the ***floor*** of the left atrium. The oblique sinus is opened by bluntly dissecting the IVC and inferior pericardium away from the right inferior vein to allow a wide opening to the posterior left atrium.

Determine the location of esophagus visualizing endoscopically with TEE in place but withdraw TEE before ablation.

Access to the dome of the left atrium is now obtained to create the exposure necessary to construct the superior connecting lesion that will join the two pulmonary vein isolations along the ***roof*** of the left atrium. Attention is now directed to the space between SVC and its attachments to the right superior pulmonary vein, and the right pulmonary artery. This space is made up of thin connective tissue and is opened by gently elevating the SVC to place this tissue on tension for optimal exposure. Using blunt dissection, this tissue is now teased away from the posterior SVC until the transverse sinus is entered. With the superior vena cava now mobilized and elevated, one should be able to advance the scope into the transverse sinus and under the ascending aorta to visualize the dome of the left atrium and typically the left atrial appendage (LAA) with the video scope.

After dissection of the area between the great vessels (the right superior pulmonary vein, the pulmonary artery and the superior vena cava) the Wolf Lumitip dissector and Glidepath are introduced in the most caudad port through the oblique sinus superiorly towards the area between

the pulmonary artery and the right superior pulmonary vein. *(Note: The clear plastic Glidepath tape is merely a leader, the other end of which attached to the inferior jaw of the bipolar radiofrequency ablation clamp).*

Once the light from the lighted dissector has been identified shining through the tissue, blunt dissection can be then used to help deliver the tip of the dissector through the pericardial reflections. ***Sharp dissection or use of the Bovie to deliver the tip should be avoided.***

Once the tip of the lighted dissector has been delivered, the Glidepath clear plastic sheath placed over the lighted dissector is now controlled with a grasper and withdrawn from the chest wall, and the lighted dissector angle is reduced while the lighted dissector is removed. This will bring the red rubber portion of the glide path into position and the tip is now connected to the end of the Synergy clamp. A purse string suture can be helpful at the skin insertion site for the bipolar clamp to maintain the pneumothorax.

Epicardial baseline testing is performed with the MAX5 to determine entrance conduction by sensing the base line electrograms originating from the heart, (alternatively, exit conduction via pacing if the subject is in normal sinus rhythm) on the right superior vein, the right inferior vein, and the crux between the superior and inferior veins. This testing routine will be repeated after the ablations have been completed.

Right-Side Ganglionated Plexi-Detection & Ablation

The MAX 5 is utilized to deliver high frequency stimulation to locate the presence of active ganglionated plexi (GP). These are located by uncovering a bradycardic response (greater than 50% increase in R-to-R interval that occurs when one stimulates directly over a ganglionated plexi). The MAX5 is then used to ablate the GPs as outlined by Jackman et. al[15] (utilizing the GP ablation map). GPs should be retested to confirm denervation is successful.

Note: At the surgeon's discretion, the surgeon may wait to perform the ganglionated plexus ablation after the right pulmonary vein antrum is isolated.

Right Pulmonary Vein Antrum Isolation

The closed AtriCure bipolar clamp (EMR2) is then introduced through the most-caudad port site, by using the Glidepath tape that is attached to the lighted dissector. By pulling the clear plastic Glidepath tape up and through the most superior port site, the inferior jaw of the clamp is then delivered behind the right-sided pulmonary veins. It is manipulated until the jaws are over the antrum of the left atrium and away from the pulmonary veins. Four (4) to eight (8) energy deliveries using the clamp are typically done to produce an electrical isolation line on the right pulmonary vein antrum.

Pulmonary vein isolation/block will be defined as pulmonary veins showing epicardial entrance and/or exit block. To assess pulmonary vein isolation (PVI), place the MAX5 or MLP1 on the pulmonary vein ensuring complete contact of the electrode with pulmonary vein tissue lateral to the PVI lesion. Check entrance block via sensing with the "Pen". If the subject is in sinus rhythm, initiate pacing to check for exit block. Repeat the ablation procedure with the bipolar clamp as necessary to achieve block.

Note: Perform the ganglionated plexus ablation at this time, if not previously performed.

Roof and Floor Lines
At this point, an MAX5 or MLP1 may be passed through the most cephalad port site and used to obtain a baseline electrogram at a point that will fall within the "box" created on the posterior wall of the left atrium. This baseline electrogram should show transmitted electrical activity from the atrium.

Note: The TEE probe should be withdrawn as a precaution against damage to the esophagus.

MCR1 and MLP1 Device Usage
Next, the MCR1 and/or the MLP1 is now introduced through a caudal port side and directed under the SVC and into the transverse sinus so that the electrodes are well positioned over the dome of the left atrium. Great care needs to be made to visualize the phrenic nerve and it is helpful to have the superior pericardial traction sutures placed on tension to make sure that the phrenic nerve is pulled well away from the electrodes.

A linear ablation is performed from the right superior pulmonary vein isolation line (PVI) across the roof of the left atrium directed towards the left superior pulmonary vein ("Roof Lesion"). In most cases when looking through the transverse sinus, the left superior pulmonary vein and left atrial appendage can be visualized. Next, a lesion is placed from the right inferior pulmonary vein isolation line (PVI) toward the left inferior pulmonary vein ("Floor Lesion"). Care should be made to ensure this lesion to intersect the right PVI line. Also, care and visualization should be utilized in making sure that this lesion is directed toward the left inferior pulmonary vein and not to the ventricle.

To decrease the risk of Atrio-Esophageal Fistula (AEF) occurrences, please use the following techniques whenever the MLP1 or MCR1 are used to ablate:

- Determine the location of the esophagus utilizing thoracoscopic visualization and the TEE probe.
- Prior to energy delivery, the Transesophageal echocardiography (TEE) probe should be retracted from the area of ablation as a measure to protect the esophagus and other surrounding tissue structures.
- **Ablation**: Ablations should be visualized, and atrial tissue should be elevated up and away from the posterior pericardium with the ablation device(s) in order to avoid collateral injury to surrounding tissue.
- **Post Ablation:** Prior to repositioning the device and prior to resting the atrium onto the posterior pericardium, the device should remain in place for 30 seconds while simultaneously quenching the device, the ablated tissue, and the surrounding tissues with saline. This will allow these areas to adequately cool.
- In addition, it is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure. [Proton Pump Inhibitors (PPIs) are recommended, however; if the patient cannot tolerate PPIs, an H2

receptor antagonist or other acid reducing agent can be prescribed.]
- Esophageal temperature monitoring will not be used during the epicardial procedure.

Completion of Right Sided Epicardial Surgical Ablation
This completes the lesions that are performed from the right endoscopic approach. At this time, the surgeon will add small radiographic clip markers at the intersection of the right superior pulmonary vein isolation and the roof lesion as well as the right inferior pulmonary vein isolation and the floor lesion to assist the EP with the location of the box lesions. The pericardium on the right side, must be closed. A chest tube is placed, the lung inflated and visualized. The ports are then withdrawn. The subject should be ventilating both lungs effectively.

Left Side Endoscopic Port Placement, Pericardial Access & Phrenic Nerve Protection
Next the subject's left side is approached, similar to the right side, but typically more posterior. Working through these ports, the left lung is deflated, and the pericardium is visualized. The phrenic nerve is visualized, and the pericardium is now gently grasped and opened typically inferior to the phrenic nerve. As on the right side the opening of the pericardium and the extension of the opening need to be done with great care to not injure the phrenic nerve. The pericardiotomy is now extended both superiorly and inferiorly. By opening the pericardium inferior to the phrenic nerve, one can extend the pericardiotomy more posteriorly than on the right facilitating the exposure of the inferior LA. Superiorly, the pericardium is opened to above the left superior pulmonary vein to provide exposure to the dome of the left atrium and the left atrial appendage.

When extending the incision cephalad, care must also be taken not to injure the recurrent laryngeal nerve as it courses beneath the aorta.

Traction sutures are frequently not necessary on the left side, but if needed they can be placed to optimize exposure if indicated. Again, these sutures need to be placed with great care to not injure the phrenic nerve.

Electrical Assessment of Left Pulmonary Veins, Ganglionated Plexi & Ligament of Marshall Division
Using the video scope, one should be able to visualize the right sided roof lesion through the transverse sinus. The MAX5 is placed and baseline electrograms from the pulmonary veins are recorded. High frequency stimulation is then performed to locate any active ganglionated plexi and their positions are noted and ablated as described below. Following this, the Ligament of Marshall may be divided.

The MID1 and Glidepath tape is introduced and directed around the left pulmonary veins with the illuminated tip surfacing just medial to the point of the divided Ligament of Marshall. The Glidepath tape is then withdrawn as a pulley around the pulmonary veins.

Left Pulmonary Vein Antrum Isolation & Ganglionated Plexi Ablation
The EML2 is attached to the Glidepath tape and then introduced through the most caudad port site. Using the Glidepath tape, the inferior clamp jaw is introduced behind the pulmonary veins. Care must be taken to always visualize the top jaw of the clamp during placement. After advancement of the clamp, the entire pulmonary vein antrum is included into the jaws. The clamp

is closed on the pulmonary vein antrum with four (4) to eight (8) energy applications are delivered, changing the position of the clamp each time. The clamp is withdrawn and the MAX5 and MLP1 is again introduced. Sensing in the pulmonary veins should now show electrical silence indicating entrance block so that no atrial electrical activity is transmitted into the veins. Alternatively, if the subject is in sinus rhythm, one can pace in the pulmonary veins and look for exit block.

Note: Pulmonary vein isolation/block will be defined as pulmonary veins showing entrance and/or exit block.

Left Sided Ganglionated Plexi Ablation
Additionally, the MAX5 and/or MLP1 is used to stimulate the areas where active Ganglionated Plexi were previously located. If these sites have not been ablated by the application of the clamp, they may now be ablated by applying radiofrequency energy through the pen device.

Completion of Roof & Floor Lesions to Connect Right and Left Pulmonary Vein Isolation Lesions, Connecting Line from LSPV to LAA
The clamp is withdrawn and the MLP1 and/or MCR1 is introduced through a caudad port site. The left atrial appendage and the pulmonary artery are retracted for better visualization into the transverse sinus. One should readily see the Roof lesion line created from the right side as it is directed towards the left superior pulmonary vein.

The MCR1 and/or the MLP1 is now used to complete the roof lesion so that it connects the right superior pulmonary vein isolation (PVI) line over to the left superior pulmonary vein isolation (PVI) line. Likewise, the Floor lesion coming from the right inferior pulmonary vein isolation (PVI) line is now fully extended to the left inferior pulmonary vein isolation (PVI) line, thus boxing out the posterior wall.

To decrease the risk of Atrio-Esophageal Fistula (AEF) occurrences, please use the following techniques whenever the MLP1 or MCR1 are used to ablate:

- Determine the location of the esophagus utilizing thoracoscopic visualization and the TEE probe.
- Prior to energy delivery, the Transesophageal echocardiography (TEE) probe should be retracted from the area of ablation as a measure to protect the esophagus and other surrounding tissue structures.
- **Ablation**: Ablations should be visualized, and atrial tissue should be elevated up and away from the posterior pericardium with the ablation device(s) in order to avoid collateral injury to surrounding tissue.
- **Post Ablation:** Prior to repositioning the device and prior to resting the atrium onto the posterior pericardium, the device should remain in place for 30 seconds while simultaneously quenching the device, the ablated tissue, and the surrounding tissues with saline. This will allow these areas to adequately cool.
- In addition, it is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure. [Proton Pump Inhibitors (PPIs) are recommended, however; if the patient cannot tolerate PPIs, an H2 receptor antagonist or other acid reducing agent can be prescribed.]

- Esophageal temperature monitoring will not be used during the epicardial procedure.

The left atrial posterior wall isolation should be assessed via sensing and/or pacing maneuvers. To do so, place the MAX5 or MLP1 and assess for entrance and/or exit conduction block. To demonstrate block, there should be no atrial electrical activity inside the left atrial posterior box or unable to pace and capture outside the box. The MAX5 is advanced and directed toward the center of the box in order to confirm absence of atrial electrical activity. This indicates "entrance block." In normal sinus rhythm, the MAX5 should be used to pace the heart from within the posterior box. (With the pacing device set at 20 beats per minute faster than the subject's intrinsic rate.) The output of the pacing device should be increased to maximal output of 20 milliamperes (mA). If pacing is unable to capture this should confirm "exit block." If the box is not complete, at this time additional lesions may be necessary.

Note – it is only possible to demonstrate bi-directional (i.e., entrance and exit) block in a subject in sinus or other paceable rhythm. If the subject is in atrial fibrillation, pacing is not possible and only entrance block will be used to demonstrate conduction block.

Lastly, using the MAX5 and/or MLP1 and/or the MCR1, a connecting lesion is made from the LSPV to the base of the LAA.

At this time, the surgeon will add small radiographic clip markers at the intersection of the left superior pulmonary vein isolation and the roof lesion as well as the left inferior pulmonary vein isolation and the floor lesion to assist the EP with the location of the box lesions.

5.1.6 Left Atrial Appendage (LAA) Exclusion

The left atrial appendage should be managed using the AtriClip PRO (PRO1 or PRO2) device. Only if the surgeon deems that the AtriClip Pro device is not able to be utilized for Left Atrial Appendage exclusion because of anatomical limitations, the surgeon may utilize a stapling device in accordance with surgical standard of care (SOC). If the surgeon determines it is not feasible or safe to address the LAA, the appendage may be left intact.

General Placement of the AtriClip PRO:
The PRO1 is introduced into the chest through the incision (the PRO2 fits through a trocar) at the 6th or 7th intercostal space directing it toward the base of the Left Atrial Appendage. Using soft endoscopic forceps or a Kitner in the surgeon's right hand, the open AtriClip device is passed over the tip of the left atrial appendage. The tip of the appendage is gently teased into the AtriClip. The device is then lowered into the base of the appendage. The skillful manipulation of the endoscope will allow the surgeon to see all angles and visualization surrounding structures and assess whether the appendage is fully contained within the AtriClip. Awareness of the proximity of the circumflex artery and its relationship to the targeted location at the base of the left atrial appendage is critical. Using the transesophageal echo (TEE) to help guide placement, the AtriClip is applied on the left atrial appendage ensuring the alignment and complete closure of the LAA. Refer to the IFU for proper AtriClip size selection.

AtriClip Deployment at Base of LAA

When the surgeon is satisfied with the AtriClip position, the surgeon releases the activation lever on the device, allowing the AtriClip to close upon the appendage. At this point, it is important to identify the subject's QRS electrograms to ensure that there are no QRS changes, and no coronary vessels have been occluded. Transesophageal echo (TEE) is examined to ensure that the entire appendage is included within the AtriClip and there is no blood flow to the appendage. A TEE with Doppler will be performed to verify exclusion of the LAA and assess for any residual pouch and also evaluate the base of the LAA along the entire length and depth of the excluded appendage. If not completely excluded, the AtriClip is re-opened and re-deployed. When the AtriClip is satisfactorily positioned around the base of the appendage, the deployment tab is pulled on the applier to fully deploy the AtriClip to the base of the left atrial appendage.

Once deployed, carefully squeeze the activation lever to retract the pull bar against the loop. Providing counter pressure on the AtriClip per the surgeon's discretion, carefully remove the applier deployment loop from the LAA, leaving the AtriClip undisturbed. Gently remove the AtriClip applier device from the thoracic cavity.

After placing the AtriClip LAA Exclusion Device on the Left Atrial Appendage and removing the deployment tool, the surgeon will place the Isolator Pen (MAX5) near the Apex of the LAA. The ASU/ASB dial will be set to PSS on the O.R. lab and the Pen will sense for atrial electrograms. The surgeon will then ask the O.R. lab operator to initiate pacing while the pen is in contact with the Apex of the LAA if the patient is in sinus rhythm. Pacing should be performed at 20 BPM above the intrinsic rate. Electrical isolation of the LAA from the Left Atrium is confirmed if there are no atrial electrograms present during sensing from the LAA or there is no capture during pacing, i.e., the heart rate stays constant and does not equal the pacing rate.

Surgical Stapler Method

The surgeon should introduce a stapling device and carefully position it around the base of the LAA. Using the transesophageal echo (TEE) to help guide placement, the stapler is closed on the base of the atrial appendage and it is amputated. The amputated LAA is withdrawn from the stapler. A TEE should be performed to evaluate the base of the LAA along the entire length and depth of the excluded appendage. If it is determined that exclusion is not complete (i.e., there is blood flow between the LAA and the LA at any point), additional thoracoscopic methods such as sutures or clips may be used to exclude the LAA completely.

Closure & Epicardial Procedure Completion

The pericardium may be re-approximated with a single suture using a laparoscopic suturing device such as the commercially available Endo Stitch™ device. If closure of the pericardium seems to be putting any tension on the deployed AtriClip, this step is not performed. A chest tube is placed, the lung inflated and visualized. The ports are then withdrawn. The subject should be ventilating both lungs effectively. Sterile dressings are applied.

Restoration of Sinus Rhythm

If the subject is not in sinus rhythm at the end of the epicardial surgical procedure, electrical cardioversion may be performed, at the discretion of the surgeon, understanding that these subjects are not typically anticoagulated at this time. The subject is then transferred to the post-operative care ward.

Post Epicardial Surgical Procedure - Subject Assessment

To assess the subject status with regard to potential bleeding, assessments of hemoglobin and

hematocrit shall be performed post-surgical ablation procedure.

Esophagoscopy
An esophagoscopy must be conducted and/or obtained **between 24-72 hours** following the Epicardial Surgical Ablation Procedure. (Refer to Protocol Section 7.0 Subject Visit 3 for details.)

5.1.7 Post Epicardial Surgical Ablation Procedure - Antithrombotic Therapy

To protect subjects from bleeding or thromboembolic events, a suggested process for antithrombotic therapy is provided as outlined below. Investigators may utilize their institutional procedures for anticoagulation/antiplatelet therapy, in recognition of various oral anticoagulants available as well as individual subject factors such as $CHADS_2$ or $CHA_2DS_2VAS_c$ score.

Within 24 Hours Post Epicardial Surgery Procedure
Within 24 hours after the surgical procedure, it is recommended that a heparin drip be restarted based on subject tolerance. When appropriate, heparin should be reduced and replaced with oral anticoagulant therapy in accordance with institutional SOC. The use of enoxaparin sodium (Lovenox) is not permitted.

Longer Term Follow-Up Post Epicardial Surgery Procedure
Oral anticoagulant therapy with warfarin (Coumadin) or another oral anticoagulant agents (NOACs) are recommended for all subjects until the Endocardial EP Ablation Procedure.

Note: If the subject does not undergo the subsequent Endocardial EP ablation procedure, per the HRS AF expert consensus statement

- Discontinuation *of oral anticoagulant therapy (e.g., warfarin) post ablation is generally not recommended in subjects who have a CHA_2DS or $CHA_2DS_2VAS_C$ score of ≥2.*
- *The* decision *regarding the use of oral anticoagulant therapy (e.g., warfarin) for longer than two (2) months following ablation should be made by the physician, based on the subject's risk factors for stroke and not on the presence or type of AF.*

To monitor anticoagulation for subjects on the following anticoagulation therapy, the following laboratory tests are recommended and should be measured at each follow up visit according to institutional SOC. Any additional anticoagulation testing may be performed according to institutional SOC or the physician's discretion.

- warfarin (Coumadin) - International Normalized Ratio (INR)
- dabigatran (Pradaxa) - when necessary utilize aPTT or ECT to assess for anticoagulant activity.
- apixaban (Eliquis) - no need to monitor anticoagulation effect, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of apixaban may be appropriate. The Chromogenic anti-Factor Xa chromogenic assays are preferable to the PT test because they yield more accurate results but may be used in emergency situations when an anti-Factor Xa assay is not available.
- Rivaroxiban (Xarelto) - routine measurement of Rivaroxiban plasma levels or its pharmacodynamics effects is not required or recommended. The Chromogenic anti-Factor Xa chromogenic assays are preferable to the PT test because they yield more accurate results but, may be used in emergency situations when an anti-Factor Xa assay

is not available.

5.1.8 Post Epicardial Surgical Procedure - Antiarrhythmic Medication Therapy

Subjects may be placed on a Class I or III AAD from the time following the surgical ablation procedure through the time of their Endocardial EP Ablation Procedure utilizing institutional practices, understanding that a washout period should be utilized for each medication, as appropriate. Amiodarone may be used immediately following the surgical procedure (up to one (1) day post procedure).

5.2 1st Blanking Period - Epicardial Surgical Ablation Procedure through Endocardial EP Ablation Procedure

Atrial Flutter and Atrial Tachycardia during First Blanking Period
Subjects that are in atrial fibrillation following the surgical procedure are to be treated with medication therapy prior to their EP procedure. Subjects will only be treated with a catheter ablation within the 90 Day blanking period if the subject has a non-manageable atrial tachycardia. At this time, the subject will receive the full Endocardial EP Ablation Procedure. The timing of this procedure will facilitate a new visit window timeline for the subject**. Please contact AtriCure to receive a new visit window timeline.** This will be documented in the eCRF.

5.3 Endocardial EP Ablation Procedure

All subjects should return between Day 91 – Day 121 to have the Endocardial EP Ablation Procedure performed by the Electrophysiologist. Standard cardiac electrophysiologic techniques will be used for mapping, ablation, and arrhythmia induction.

RF based, irrigated, power controlled, ablation catheters for endocardial lesions must be used for endocardial left sided catheter ablation; no other device should be used for ablation purposes in the left atrium. During ablation, it is recommended that power not exceed 50 watts and 35 watts, if the catheter is perpendicular to the tissue. Refer to the relevant Instructions for Use for further details.
The use of phased array intracardiac ultrasound (ICE) during the procedure is encouraged to guide the transeptal puncture and catheter ablation process.

Note: Transesophageal echocardiography (TEE) is used during the Endocardial EP Ablation Procedure. The transesophageal echocardiography probes should be retracted from the area of ablation prior to energy delivery as a measure to protect the esophagus and other surrounding tissue structures.
Note: The order of the below EP procedure (e.g., right-to-left or left-to-right) may be performed according to institutional practices. However, the electrophysiologist should bear in mind the following:

- *Monitoring for cavo-tricuspid isthmus lesion and mitral isthmus lesion re-conduction after 20 minutes or longer following initial lesion creation is required.*
- *Heparin shall be administered to maintain an ACT of > 300 seconds prior to any left atrial catheter-based ablation maneuvers.*

Note: electroanatomic mapping is required using Multipolar catheters (e.g., Lasso System)

5.3.1 Pre-Endocardial EP Ablation Procedure

Each subject should return between Day 91 – Day 121 to have the Endocardial EP Ablation Procedure performed by an Electrophysiologist.

Pre-Endocardial EP Ablation Procedure Subject Assessment
Pre-procedure data must be collected prior to starting the EP ablation procedure. See **Visit 5** for a detailed description of data to be collected.

Pre-Endocardial EP Ablation Procedure Proton-Pump Inhibitor (PPI) Therapy
It is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure.

Patient Review
Review will be conducted with patient regarding AEF warning signs and treatment with review of the patient emergency wallet card and patient educational brochure.

Pre-Endocardial EP Ablation Procedure Antiarrhythmic Medications
If subject was placed on an AAD following the surgical procedure, it is recommended that the AAD should be discontinued for at least five (5) days (or 5 half-lives) prior to performing the EP catheter procedure to allow adequate drug washout (amiodarone should be discontinued 45 days prior to the Endocardial EP Ablation Procedure).

Pre-Endocardial EP Ablation Procedure Antithrombotic Medications
To protect subjects from bleeding or thromboembolic events, investigators may utilize their institutional procedures for anticoagulation/antiplatelet therapy, in recognition of various oral anticoagulants available as well as individual subject factors such as $CHADS_2$ or CHA_2DS_2VASc score.

Subjects may undergo their Endocardial EP Ablation Procedure on therapeutic levels of their oral anticoagulant (e.g., INR 2.0 - 2.5 for warfarin held for 12-24 hours prior to the procedure or based on institutional SOC) in order to protect against thromboembolic events.

5.3.2 Subject Preparation for Endocardial EP Ablation Procedure

The subject is brought to the Electrophysiology (EP) Laboratory. Either conscious sedation or general anesthesia may be used, per institutional SOC. The subject is prepped and draped according to institutional SOC, to allow access to femoral, jugular, and /or other access sites as needed.

Measures to Protect the Esophagus and Phrenic Nerve Structures during the Endocardial EP Ablation Procedure

During the endocardial procedure, standard institutional techniques should be utilized to mitigate, to the extent possible, any potential collateral injury to the esophagus and phrenic nerve structures as a result of ablation. These techniques may include, but are not limited to, the following:

- Use of intracardiac ultrasound (ICE) or transesophageal echocardiography (TEE) to guide the catheter ablation process. Note: Transesophageal echocardiography probes should be retracted from the area of ablation prior to energy delivery as a measure to protect the esophagus and other surrounding tissue structures.
- Use of an esophageal temperature probe, positioned under fluoroscopy such that it is as close to the tip of the ablation area as possible.
- Register Baseline CT/MR image with electroanatomic mapping system, to define anatomic structures.
- Phrenic Nerve Mapping. Prior to energy delivery near the ostium of the right superior pulmonary vein, SVC, or roof of LAA, perform pacing to identify phrenic nerve location relative to planned ablation site(s).
    - Pacing at high output (e.g., 10 mA) is recommended.
    - If a 3-dimensional electroanatomic mapping system is used, sites where diaphragmatic pacing is documented should be noted on the map.

Catheter Conduction Block Assessment & Ablation Steps
The following checklist of the arrhythmia assessment and catheter ablation steps to be performed by the Electrophysiologist is provided below:

Diagnostic Endocardial EP Ablation Procedure Placement
Insert multi polar Coronary Sinus (CS) catheter into coronary sinus for standard EP mapping and ablation techniques. Also, a multi electrode diagnostic HIS catheter may be placed in position for help in guidance of CS cannulation and transeptal puncture at physician's discretion.

Cavo-tricuspid Isthmus Lesion (CTI)
If subject has undergone prior catheter ablation for atrial fibrillation or Atrial Flutter, this lesion line may have been created at the time of previous ablation. In this instance, the EP should check for bidirectional cavo-tricuspid isthmus block, and, if required, perform additional cavo-tricuspid isthmus ablation.

The cavo-tricuspid isthmus lesions are created according to standard institutional practices. Check for bidirectional cavo-tricuspid isthmus block should be performed on all subjects and re-checked after a standard waiting period of 20 minutes.

Check Conduction Block of Epicardial Surgical Lesions
Using a circular mapping catheter, check for both right and left pulmonary veins isolation for entrance and exit block. Check the Posterior Box for entrance and exit block. This is typically performed using the ablation catheter; however, this may also be achieved utilizing a voltage map with a 3-D mapping system.

Gap Closure
Note: If block has not been achieved, it is required for the electrophysiologist to deliver additional ablations to the targeted site in an effort to achieve block (i.e., "gap closure"). If additional energy delivery is performed, the lesion must be rechecked for block.

If an atrial arrhythmia is present/induced during conduction block testing, then it should be mapped and ablated. If atrial fibrillation (AF) is induced, then complex fractionated atrial electrogram (CFAE) mapping and ablation may be performed.

Note: limit of 2 hours for total CFAE mapping and ablation per Endocardial EP Ablation Procedure and no more than 30cc of saline per minute with a maximum of 4 liters of saline administered for the entire Endocardial EP Ablation procedure.

Mitral Isthmus Lesion
Note: If the subject presents to the Endocardial EP Ablation Procedure in mitral isthmus dependent Atrial Flutter ("Peri-Mitral Flutter"), the mitral isthmus line must be completed by the Electrophysiologist.

The literature suggests that this will be necessary in only 15-20% of subjects.

Note: Proof of block in the box and bilateral pulmonary vein isolation should be assessed before any mitral line is initiated.

The mitral isthmus line will be initiated by the electrophysiologist from an endocardial access at the time of the Endocardial EP Ablation Procedure only if the subject presents with mitral isthmus dependent atrial flutter at the time of the EP procedure.

The maneuver will be facilitated by crossing the interatrial septum and placing an ablation catheter at the mitral valve annulus and withdrawing to the left inferior pulmonary vein isolation (PVI) line or the inferior floor line, completing the mitral isthmus line. Lesions in the coronary sinus may be needed to complete this lesion.

(Note: If the EP is unable to complete the Mitral isthmus line from this posterior approach, the EP may utilize a more anterior approach. The Mitral Line will be performed entirely by the electrophysiologist during the Endocardial EP Ablation Procedure).

Re-check Conduction Block of Mitral Isthmus Lesions
Re-check bidirectional block of Mitral Isthmus Lesion should be assessed after 20 minutes following completed ablation.

Definition of Conduction Block
For this study, endocardial entrance and exit block via pacing maneuvers will be used to assess pulmonary vein isolation and left atrium posterior wall isolation. Pulmonary vein isolation/block will be defined as pulmonary veins showing endocardial entrance and exit block with either a lasso (circling mapping catheter) or other multipolar catheters. Endocardial bidirectional block via pacing maneuvers will be used to assess the cavo-tricuspid isthmus and mitral isthmus lesions. Particular attention should be paid to block across the mitral isthmus line.

Note: It is only possible to demonstrate bidirectional (i.e., entrance and exit) block in a subject in sinus or other paceable rhythm. If the subject is in atrial fibrillation, they will not be able to be paced and only entrance block will be used to demonstrate conduction block. Utilization of local capture should be the goal, understanding that this may not always be demonstrated.

Isoproterenol or Adenosine Testing (Optional)
Per investigator discretion, once confirmation of block, or following mapping and ablation of atrial flutter or CFAEs to address AF, isoproterenol or adenosine may be administered based on institutional practices.

Complex Fractionated Atrial Electrogram (CFAE) Ablation
Complex fractionated atrial electrogram (CFAE) mapping and ablation may be performed if atrial fibrillation is induced following completion of the lesion set.

Note: limit of 2 hours for total CFAE mapping and ablation per Endocardial EP Ablation Procedure and *more than 30cc of saline per minute with a maximum of 4 liters of saline administered for the entire Endocardial EP Ablation procedure.*

For purposes of this protocol, complex fractionated atrial electrograms are defined as:
(1) atrial electrograms with two or more deflections with fractionated baseline complexes, with continuous activity over a 10-second recording time; or
(2) atrial electrograms with a cycle length ≤ 120 ms over a 10-second recording time[16, 17].

The ablation catheter must be in stable position when recording these electrograms. A visual inspection approach (i.e., a standard EP recording system with the ablation catheter in stable position for 10 seconds to record the CFAE and capture the raw data from the procedure) will be used[18 19]
.

Note: For purposes of this study, representative intracardiac electrograms at each target CFAE site should be recorded (both pre- and post-ablation).

Note: Investigational sites should review annotated pre-ablation electrogram recordings of ablated CFAE(s) to confirm whether the local CFAE met the protocol-definition of CFAEs (as defined above). This activity may be performed following completion of the EP procedure, given the potential to unduly extend procedure time as a result of performing this analysis during the procedure.

Identified local CFAE(s) may be ablated using the RF based, irrigated, power controlled, ablation catheters for endocardial lesions. During ablation, it is recommended that power not exceed 50 watts and 35 watts if the catheter is perpendicular to the tissue. Refer to the relevant Instructions for Use for further details.

The objectives for CFAE ablation are as follows:
- Technical criterion: Eliminate local CFAE (i.e., post-ablation CFAE electrogram recording is abolished as compared to pre-ablation CFAE electrogram recording).
- Procedural criterion: Termination of atrial fibrillation to either organized atrial tachycardia or sinus rhythm. If local CFAE(s) are eliminated, but the arrhythmia continues as organized atrial flutter or atrial tachycardia, the atrial arrhythmia should be mapped and ablated, with the ultimate goal of attaining sinus rhythm. Complex fractionated atrial electrogram (CFAE) mapping and ablation may be performed and stopped upon conversion to sinus rhythm (confirmed by isoproterenol testing). Alternatively, if sinus rhythm is not obtained, cardioversion is acceptable to convert the subject to sinus rhythm.

5.3.3 Endocardial EP Ablation Procedure Completion

Once all catheter maneuvers are complete, EP mapping and ablation catheters are withdrawn. Catheter insertion site hemostasis and dressings should be performed according to institutional

techniques.

The subject is awakened and extubated, at the discretion of the electrophysiologist in consultation with the anesthesiologist, if general anesthesia was used. The subject is transferred to the recovery area.

5.3.4 Post Endocardial EP Ablation Procedure & Longer-Term Antithrombotic Therapy

To protect subjects from either post-surgical bleeding or thromboembolic events, a recommended process for antithrombotic therapy is provided as outlined below. Investigators may utilize their institutional procedures for anticoagulation/antiplatelet therapy, in recognition of various oral anticoagulants available as well as individual subject factors such as $CHADS_2$ or $CHA_2DS_2VAS_c$ score.

Within 24 Hours Post– Endocardial EP Ablation Procedure
If oral anticoagulants were stopped prior to the EP procedure, or INR levels decrease to < 2.0, the Investigator should determine the potential need for anticoagulant therapy in accordance with institutional SOC based upon subject characteristics. Intravenous unfractionated heparin may be used as a bridge to resumption of INR 2.0 – 3.0. Alternatively, a direct thrombin or Factor Xa inhibitor can be administered following ablation. Regardless, the investigators should be mindful of risks for bleeding and balance against the potential for thromboembolism, in the post-ablation setting. For subjects who undergo their EP procedure with therapeutic levels of their oral anticoagulant, the oral anticoagulant may be resumed. The use of enoxaparin sodium (Lovenox) is not permitted. Management of anticoagulation therapy should be in keeping with the best practice of the Institution during the peri-operative period.

Longer Term Follow-Up Post Endocardial EP Ablation Procedure
Oral anticoagulant therapy such as warfarin or dabigatran is recommended for all subjects for at least three (3) months following the EP procedure. The decision regarding the use of oral anticoagulant therapy for longer than 3 months following ablation should be made by the physician, based on the subject's risk factors for stroke and not on the presence or type of AF.
Note: Discontinuation of oral anticoagulation therapy (e.g., Warfarin) post-ablation is generally not recommended in subjects who have a $CHADS_2$ or $CHA_2DS_2VAS_c$ score ≥ 2.

To monitor anticoagulation for subjects on the following anticoagulation therapy, the following laboratory tests are recommended and should be measured at each follow up visit according to institutional SOC. Any additional anticoagulation testing may be performed according to institutional SOC or the physician's discretion.

- warfarin (Coumadin) - International Normalized Ratio (INR)
- dabigatran (Pradaxa) – when necessary utilize aPTT or ECT to assess for anticoagulant activity.
- apixaban (Eliquis) - no need to monitor anticoagulation effect, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of apixaban may be appropriate. The Chromogenic anti-Factor Xa chromogenic assays are preferable to the PT test because they yield more accurate results but may be used in emergency situations when an anti-Factor Xa assay is not available.
- Rivaroxiban (Xarelto) - routine measurement of Rivaroxiban plasma levels or its pharmacodynamics effects is not required or recommended. The Chromogenic anti-

Factor Xa chromogenic assays are preferable to the PT test because they yield more accurate results but, may be used in emergency situations when an anti-Factor Xa assay is not available.

5.3.5 Post EP Procedure (2nd Blanking Period) Antiarrhythmic Medication Therapy – AAD Management and Recommended Guideline

Following the EP ablation procedure, a subject may be continued on an AAD for up to 90 days (which shall be called the Post Endocardial EP ablation procedure blanking period). If the subject is in sinus rhythm at the 3-month post endocardial EP ablation procedure, the subject's AAD therapy will be discontinued. If the atrial arrhythmia returns, the subject may be returned to AAD therapy utilizing an AAD that the subject previously failed at a dose not exceeding those previously failed from baseline. The 3-month period between the blanking period and the 6-month visit will be utilized for AAD medication optimization. An arrhythmia will not be considered an effectiveness failure during this time period. AAD medication must be optimized prior to the 6-month visit, at which time any arrhythmias will be counted towards the effectiveness endpoints. At the 6-month visit, if the subject is in sinus rhythm on a previously failed AAD at a dose not exceeding previously failed, the subject may remain on the AAD.

Re-ablation to treat Atrial Fibrillation, Atrial Tachycardia, and Atrial Flutter following Endocardial EP Catheter Ablation
Subjects that experience atrial fibrillation, atrial tachycardia, or atrial flutter may be treated with a catheter ablation if deemed medically necessary following the Endocardial EP Ablation Procedure.

Second Blanking Period Catheter Ablation
- Subjects that experience a non-manageable, atrial fibrillation, atrial tachycardia and atrial flutter within the blanking period may be treated with an additional catheter ablation.
- An ablation of an atrial fibrillation, atrial tachycardia and atrial flutter would not be considered a failure within the blanking period.
- Re-intervention is encouraged to be performed during the 90-day blanking period but may be performed anytime during the study if deemed medically necessary.

6.0 IDENTITY OF STUDY DEVICES

This IDE study is investigating the AtriCure Bipolar System (Figures 3-81) used for performing the minimally invasive ablation surgery in conjunction with commercially available ablation catheters as described in further details below.

Left Atrium

Ablation catheters used for endocardial lesions in the left atrium (referred to as "LA ablation catheters") should be:
- RF based
- Irrigated
- Power controlled

For gap closure (as needed) and creation of the mitral isthmus lesions and CFAE ablation, the RF based, irrigated, power-controlled ablation catheter shall be used in a consistent manner as outlined in the product Instructions for Use.

Right Atrium

Ablation catheters used for endocardial lesions in the right atrium (referred to as "RA ablation catheters") should be:

- RF based
- Irrigated or non-irrigated
- Power controlled or temperature controlled

Further, the procedure should incorporate electro-anatomic mapping. The electrophysiologist may also use additional commercially approved catheters for the cavo-tricuspid isthmus lesion, at the physician's discretion. The use of cryo balloon catheters will not be permitted. Electrophysiologists may use irrigated or non-irrigated RF ablation catheters, depending on the Electrophysiologist's preference.

AtriCure Bipolar System

The AtriCure Bipolar System used in this clinical study consists of a radiofrequency (RF) generator (Ablation Sensing Unit, model ASU2, AtriCure) (**Figure 3**), a switchbox console (ASU Source Switch or matrix, model ASB3) (**Figure 3**), two (2), single use, bipolar RF clamp (models EMR2 and EML2) (**Figure 4**), three (3) single use bipolar RF Pens: the Isolator Long Pen TT (model MAX5), the Coolrail Linear Pen (model MCR1), the Isolator Linear Pen (model MLP1) (**Figures 5, 6, 7 respectively**); the Glidepath Tape (accessory)(model GPT100) (**Figure 8**); and the AtriClip PRO LAA Exclusion System (PRO1 or PRO2) (**Figures 9 and 10**).

6.1 Generator and Switch Matrix

The Ablation and Sensing Unit (ASU2) is a radiofrequency (RF) generator used to power AtriCure Devices which include the Isolator Synergy Clamps, Isolator Long Pen TT, and Coolrail Linear Pen, and the Isolator Linear Pen. The ASU2 is a portable, reusable device that produces and delivers bipolar RF energy near the AM frequency band. The device consists of a main printed circuit board, Power Entry Module, Footswitch Interface, and Feedback Indicators contained within a box enclosure. The ASU2 controls and delivers the voltage and current output to the device and determines the duration of each ablation. The footswitch is the input device used to activate RF energy delivery. When the footswitch is activated (depressed) the ASU2 provides power to the selected devices according to a predefined algorithm. Upon reaching the predetermined threshold (voltage and/or current relationship) the ASU2 will light a visual indicator and sound an audible tone signaling the end of the ablation cycle. RF energy output may also be terminated by the user by releasing the footswitch.

The ASU2 is used in conjunction with the Switch Matrix (ASB3). The ASB3 is an accessory interface module or source switch allowing various AtriCure devices to connect to the ASU2 at the same time. A total of 3 devices may be connected to the ASB3 simultaneously but power is delivered to only one device at a time as determined by the user. The device to be used (powered) is selected by turning the rotary switch on the front panel of the ASB3.

Both the ASU2 and ASB3 consoles are cleared for use with the EMR2 and EML2 model clamps to ablate cardiac tissue during surgery via 510(k) submission K101174. The ASU2 was cleared

for use with the Isolator Long Pen TT (MAX5) for the cardiac ablation indication via 510(k) submission K050459. The ASU2 and ASB3 are cleared for use with the Isolator Linear Pen for cardiac tissue ablation indication via 510(k) submission K100501. The ASU2 and ASB3 are also cleared for use with the Coolrail Linear Pen for the ablation of cardiac tissue under K073605.

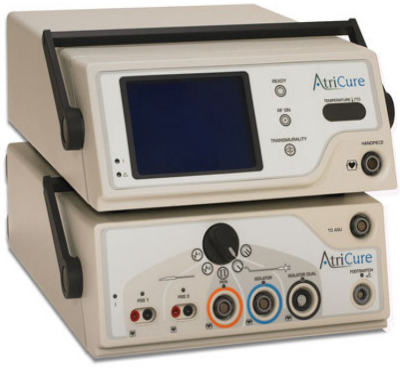


Figure 3: RF Generator and Source Switch: AtriCure, Inc. Model ASU2/ASB3

6.2 Isolator Clamps (EMR2 and EML2)

The clamp hand pieces resemble a standard surgical clamp and are always under the direct control of the surgeon. The hand pieces are available in multiple configurations to aid in accessing tissues and for user preference.

The hand pieces proposed for this study are: Isolator Synergy Clamps - available in models EMR2, a clamp which curves to the right, and EML2, a clamp that curves to the left. Both models were first cleared for cardiac tissue ablation via 510(k) submission K101174.

The proposed clamps deliver the same bipolar RF energy which is delivered via electrodes housed within the insulating jaws of the clamps. The devices differ only in geometry of the jaws and in the mechanism for closing the device jaws. Comparative bench and animal testing for the proposed devices supporting their safe and effective use has been submitted to FDA in 510(k) submissions.

The clamps all have two parallel pairs of electrodes on the device jaws, and an in-line handle with syringe- type actuation and button release mechanism. The electrode pair is formed by two opposing, linear electrodes, one on each opposing jaw of the clamp. The electrodes on each jaw are spaced 0.5 mm (0.02”) from the center line of the jaw and 1.0 mm (0.04”) apart from each other. The bipolar RF energy is delivered between directly opposing linear electrodes in the electrode pair. Alternating current flows from the proximal electrode of an electrode pair located on the inner surface of the top insulated jaw to the distal electrode of an electrode pair located on the opposing surface of the bottom insulated jaw. RF energy is delivered to one electrode pair at a time; each pair functions completely independently of the other. Since the bipolar RF energy delivery switches or alternates between each electrode pair, the mode of and amount of energy delivery per unit volume of tissue clamped between the jaws of the hand piece is equivalent to that of the single electrode clamp handpiece.

The jaws of the EMR2 and EML2 curve to the right and left, respectively, to aid the surgeon in

accessing the cardiac tissues. Upon closing the jaws, the proximal jaw of the end-effector closes to the distal jaw in a “pivot to parallel” motion. The jaw is passive until the aperture is closed to 8 mm at which point, the proximal jaw is in parallel with the distal jaw and remains parallel until it is re-opened.

With Glidepath tape

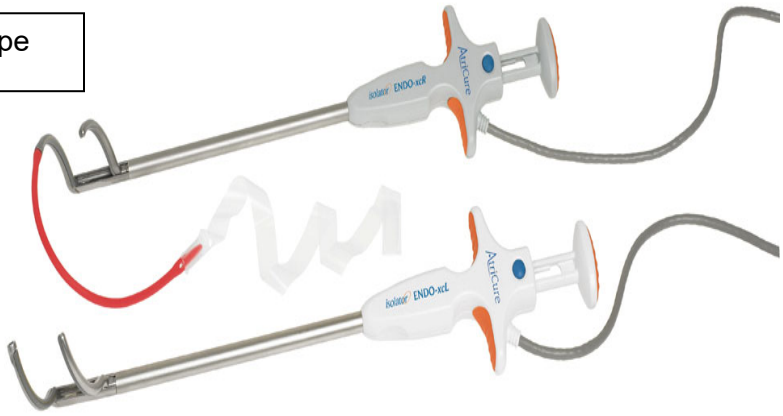


Figure 4: Left curve Isolator Synergy clamp (model EML2) and right curve Isolator Synergy clamp (model EMR2) (Investigational Device Clamps)

6.3 Isolator Long Pen TT (MAX5)

The Isolator Lon Pen TT (Pen) is a hand-held, single use, bipolar RF ablation device. The Pen was cleared for surgical ablation of cardiac tissue under K050459. The clearance for the Pen was expanded to include temporary cardiac pacing, sensing, recording, and stimulation for the evaluation of cardiac arrhythmias during cardiac surgery under K061593. The Pen is available in two configurations, the MAX1 which has a shorter shaft, and the MAX5, which has a longer shaft. The devices are identical with the exception of the length of the shaft.

The Pen resembles a standard pen or wand type ablation device and is always under the direct control and visualization of the surgeon. The Pen produces linear and spot lesions on cardiac tissue. It is designed to deliver dry bipolar RF energy to the tissue through the two electrodes on the device end effector. A handle is connected to the malleable shaft, which is connected to the end effector. Current flows from one electrode, through the tissue to the other electrode to create bipolar ablation lesions on cardiac tissue. When the Pen is connected to an auxiliary pace, sense, or stimulation device; the Pen is designed to provide temporary pacing or monitoring.

Figure 5: Isolator Long Pen TT (MAX 5)

6.4 Coolrail Linear Pen (MCR1)

The Coolrail Linear Pen (Coolrail pen) is a handheld, single use, dry, bipolar RF ablation device. The Coolrail pen was originally cleared for surgical ablation of cardiac tissue under K073605. The end effector of the Coolrail pen is longer than that of the Isolator Long Pen TT to facilitate the creation of longer linear lesions. The device is designed with internally cooled electrodes to produce continuous, full-thickness lesions on the beating heart. The fluid tubing throughout the cable and end-effector provides a closed loop of internal cooling (non-irrigated) functioning to cool the electrodes which reduces surface heating (thermal heating).

The Coolrail pen is comprised of an end effector, shaft, handle, cable, and pump system container (PSC). The end effector consists of one pair of electrodes separated with insulating material, two internally cooling fluid tubes (not in contact with tissue), thermal sensor, and sensor wires. The end effector is connected to a pivot joint. The pivot is attached to a clevis, which allows the end effector to be moved into three positions (-25°, and +25° from inline at 0°) by the user. The clevis is attached to a malleable shaft. The handle is attached to the shaft. Fluid tubes, thermistor wires, and RF signal wires pass through the malleable shaft, handle, and cable to the PSC.

The pump system container houses the fluid pump, fluid reservoir, and thermistor logic. The fluid pump is capable of pumping the fluid from the pump system container throughout the device. The fluid reservoir is capable of maintaining the pressure in the system so that the pump system can operate efficiently. The thermistor logic determines the temperature of the electrodes and shuts down the RF energy if the temperature exceeds 55°C. The thermistor is centered along the length and width of the electrodes. It is insulated from the tissue and measures the temperature of the electrodes only. The temperature threshold is set to ensure that the device is functioning properly (i.e., there is enough fluid in the system, there is no obstruction in the fluid path, and the pump is functioning properly). The light-emitting diode (LED) on the PSC will light up if the system has exceeded the temperature threshold or if the system has not been filled with fluid.

Figure 6: Coolrail Linear Pen (MCR1)

6.5 Isolator Linear Pen (MLP1)

The Isolator Linear Pen is a single subject use electrosurgical instrument designed for use only with the ASU and ASU Source Switch (ASB). The Pen is used to ablate cardiac tissues and as a surgical pacing and mapping tool and was cleared under K100501. When the Pen is connected to the ASU, the ASU provides the bipolar radiofrequency (RF) energy flowing between both electrodes of the Pen. The Operator controls the application of this RF energy by pressing the Footswitch. When the Pen is connected to an auxiliary pace, sense, or stimulation device; the Pen is designed to provide temporary pacing or monitoring.

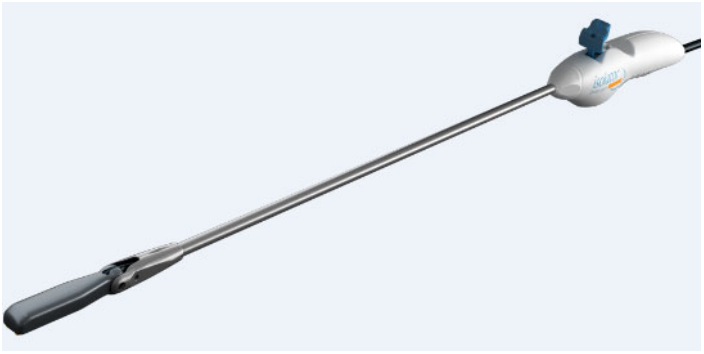


Figure 7: Isolator Linear Pen (MLP1)

6.6 Glidepath Tape (GPT100)

The Glidepath Tape (product code GPT100) is a single-use device comprised of a clear

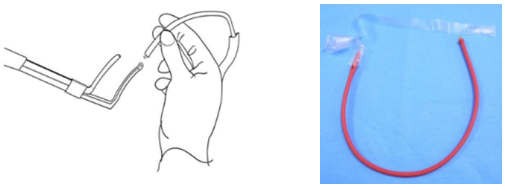


Figure 8: Glidepath Tape

polyurethane ribbon attached to a red rubber leader (Figure 4 & 8). This device is packaged with

the Isolator Clamps and may be used to aid in positioning the jaws of the clamp. One end of the Glidepath attaches the distal jaw of the Isolator Clamp, while the other may be pulled by the user to aid in positioning the jaws of the clamp in the desired location.

The GPT100 (snap-fit model) connects to the distal jaw of the EMR2 or EML2 Clamp via a snap pin (Figure 4 & 8). The GPT100 remains fixed on the EMR2/EML2 after being snapped into place.

6.7 AtriClip PRO LAA Exclusion System (PRO1 or PRO2)

The AtriClip PRO LAA Exclusion System (Figures 9 & 10) consists of a self-closing, sterile, implantable Clip which is pre-loaded on a disposable Clip applier. The AtriClip PRO1 was originally cleared under K093679. The AtriClip PRO2 was originally cleared under K160454. The frame assembly of the implantable Clip consists of two Nitinol (nickel titanium) springs connecting two opposing titanium tubes (core), which are covered with a Polyurethane elastomer. This assembly is covered with a knit braided polyester fabric, composed entirely of Polyethylene terephthalate (PET). The Nitinol springs are biased toward the closed position allowing the device to close in the absence of opposing forces (Figure 10). When closed, the Clip applies uniform pressure over the length of the Clip to ensure consistent, reproducible, and secure exclusion of the LAA. The AtriClip PRO LAA Exclusion System does not contain natural rubber latex components.

Figure 9: AtriClip PRO LAA Exclusion System [PRO1 (left) & PRO2 (right)]

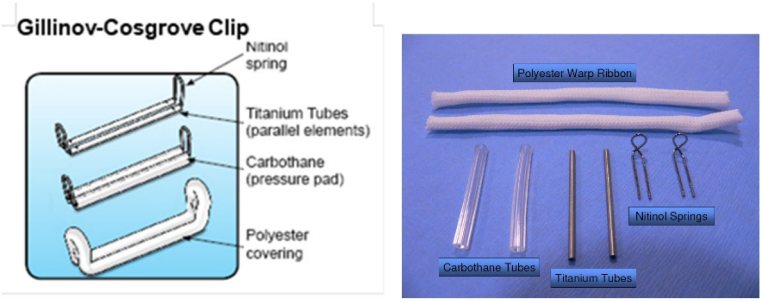


Figure 10: AtriClip LAA Exclusion Device Construction and Component

6.8 Product Accountability

The investigator will maintain a complete device inventory record for all investigational devices received by AtriCure. All shipping record receipts received with the investigative devices will be

maintained. All investigational devices that are used during each procedure will be documented.

7.0 SUBJECT VISITS

Details for specific subject visit activities are found in **Section 7.17**, **Repeated Study Visit Tests**.

7.1 Visit 1 – Baseline

Subjects will be screened for study participation during the baseline visit. The procedures required for the baseline visit may be conducted during more than one visit. The following will be conducted and/or obtained: Some baseline procedures may have been completed as patient standard of care and therefore may be completed prior to informed consent and do not need to be repeated after consent.

The following procedures must be conducted within **120 days prior** to the Epicardial Surgical Ablation Procedure:

- Transthoracic Echocardiogram (TTE) to measure Left Atrial diameter and Left Ventricular Ejection Fraction
- CT or MRI imaging of Pulmonary Veins
  Note: Based on investigator discretion and institutional practices, non-invasive coronary angiography during CT or MR imaging may also be performed.
- CT imaging of coronary anatomy should be located before the procedure to ensure the safe ablation of cardiac tissue is not impeded by the coronary anatomy (see Coronary Anomalies description/Appendix 1)

The following procedures must be conducted and/or obtained within **60 days prior** to the Epicardial Surgical Ablation Procedure:

- Lung function test in subjects with a documented medical history of pulmonary compromise

The following procedures must be conducted within **45 days prior** to Epicardial Surgical Ablation Procedure:

- Informed Consent
- Patient AEF Education
- It is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure.
- AFEQT Questionnaire
- Demographics
- Relevant Medical and Surgical History, including AF History and any pre-planned surgical procedures (note: preplanned surgical procedures will be documented in source documents only)
- NYHA Class
- Neurologic Assessment (NIH Stroke Scale and Modified Rankin Scale)

- Targeted Physical Examination which includes assessment of the following body systems: General Appearance, Cardiovascular, Respiratory, and Musculoskeletal
- Height and Weight (including BMI calculation)
- Blood Pressure and Heart Rate
- Medications Review
- Documentation of Persistent AF or Longstanding Persistent AF
  - The **AF Classification Confirmation Form** (**Appendix 2**) must be submitted to the sponsor for confirmation of subject's AF classification status prior subject treatment, per the HRS Consensus Statement.

The following procedures must be conducted within **7 days prior** to the Epicardial Surgical Ablation Procedure:

- Urine or serum Pregnancy Test - only for females of childbearing potential
- Heart Rhythm Assessment - 30 second ECG
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine, Total Bilirubin, AST/ALT (or SGOT/SGPT)
- Note: For exclusion criterion 23 in the event liver function test results (Total Bilirubin and AST/ALT (or SGOT/SGPT) do not exceed specified limits, but there remains a high suspicion of significant liver disease, the investigator may perform additional assessments as needed, based on their medical judgment.
- Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran) Review of all inclusion/exclusion criteria and determine if the subject is eligible for study participation
- Confirm Inclusion/Exclusion criteria

7.2 Visit 2 – Epicardial Surgical Ablation Procedure

NOTE: At the time of scheduling the subject's Epicardial Surgical Ablation Procedure, sites are encouraged to schedule the subject's Endocardial EP Ablation Procedure, for 91-121 days following surgery. Scheduling the Endocardial EP Ablation Procedure at the time of the subject's surgical procedure will ensure the subject's EP procedure occurs within the protocol visit window.

The Epicardial Surgical Ablation Procedure (**See Section 5.1**) will be performed within 45 days of the subject consenting to the clinical study. If the Epicardial Surgical Procedure is delayed, the subject must be re-consented and baseline tests repeated if necessary, for protocol defined windows.

The following must be conducted and/or obtained prior to or during the Epicardial Surgical Ablation Procedure:

- Confirm Inclusion/Exclusion criteria
- Esophagoscopy
- Note: Esophagoscopy to be performed prior to the placement of access ports for the epicardial procedure.
- Transesophageal Echo (TEE) – (performed at the beginning of the surgical procedure prior to placement of access ports, to confirm study eligibility and rule out thrombus in the left atrium or LAA. If a thrombus is present in the left atrium or LAA on TEE, the subject should not have the surgical ablation procedure performed.)

- Surgical Procedure Details (including procedure times)
- Surgical Ablation Details (including ablation and lesion details)
- LAA Management Details
- TEE Assessment (following exclusion of LAA)
- Adverse Event Assessment
- Post procedure Heart Rhythm Assessment – 30 second ECG
- Medications Review: Anticoagulation/antiplatelet therapy administered during surgical intra-procedure

Note: If patient requires conversion to either a thoracotomy or sternotomy during the surgical ablation procedure, they should not receive the catheter ablation procedure, and will be followed for 12 months.

7.3 Visit 3 – Post Epicardial Surgical Ablation Procedure

The following must be conducted and/or obtained between **2-3 days post** Epicardial Surgical Ablation Procedure:

- Neurologic Assessment (NIH Stroke Scale and Modified Rankin Scale)
- Targeted Physical Exam
- Medications Review
- Note: If discharging subject on AADs, care should be taken in starting any new Class III AAD (subject should return to assess for any potential adverse reaction to drug).
- Heart Rhythm Assessment - 30 second ECG
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran)
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Adverse Event Assessment
- Hospital Discharge Date

The following must be conducted and/or obtained **between 24-72 hours** following the Epicardial Surgical Ablation Procedure:

- Post- Epicardial Procedure Esophagoscopy
  The post-epicardial procedure esophagoscopy is a screening for a post ablation injury indication assessment for esophageal injury. If the esophagoscopy reveals esophageal or pericardioesophageal injury (thermal or non-thermal), that in the opinion of the physician warrants closer or additional observation because of suspected AEF, the subject can be seen using “AEF Unscheduled Visit” as often as deemed necessary by the physician.

  In the event that an esophageal or esophagopericardial injury is detected, the injury should be well described (detailed description, distance from incisors, location) and multiple quality images of the injury taken at various angles. Redacted and labeled images, reports, and relevant documents will be sent to a core lab for adjudication.

  The hospital should follow standard of care for follow-up and treatment of an esophageal

or esophagopericardial injury the following may be warranted:

- Soft mechanical diet
- Double the standard dose of proton pump inhibitors until repeat esophagoscopy indicates that esophageal or esophagopericardial injury is in remission.
- Repeat testing to confirm progression of remission by appropriate imaging (e.g., repeat esophagoscopy) recommended within 14 days of esophagoscopy.

7.4 1st Blanking Period – Epicardial Surgical Ablation Procedure through Endocardial EP Ablation Procedure

Blanking Period Arrhythmia Treatment - Treatment will only be permitted if atrial flutter could not be medically managed. The subject may only be treated during the blanking period **after** Visit 4 (30 Day Post Epicardial Surgical Ablation Procedure). The following will be conducted and/or obtained:

- Heart Rhythm Assessment – 30 second ECG
- Medications Review
- Adverse Event Assessment
- Treatment Decision
  - If a decision is made to perform the Endocardial EP Ablation Procedure during the 1st blanking period (i.e., prior to day 91-121) it is not considered an "out of window" visit. **The date of the Endocardial EP Ablation Procedure will be considered study Visit 5** and will be performed as described in **Section 5.3.**

7.5 Phone Visit (Post Epicardial Surgical Ablation Procedure)

Phone contact with the subject to be initiated by the site at **Day 18 (+/-2)** post Epicardial Surgical Ablation Procedure to evaluate presence of:

- Symptoms of AEF
- Note: If in the opinion of the physician subject requires closer or additional observation, the subject can be seen using "AEF Unscheduled Visit" as often as deemed necessary by the physician.

7.6 Visit 4 – 1 Month Post Epicardial Surgical Ablation Procedure

A follow-up evaluation will be scheduled for **one month (30 days + 7 days)** post Epicardial Surgical Ablation Procedure. The following must be conducted and/or obtained:

- Neurologic Assessment (NIH Stroke Scale and Modified Rankin Scale)
- Targeted Physical Exam (includes evaluation for symptoms of AEF)
- Weight
- Blood Pressure and Heart Rate
- NYHA Class
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Heart Rhythm Assessment – 30 second ECG
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Medications Review

- Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran)
- Adverse Event Assessment
- CT/MR imaging only if subject exhibits symptoms suggestive of pulmonary vein stenosis. (*Note: Use same imaging technique performed at baseline PV imaging to the extent possible.*
- AAD Washout period leading into Endo procedure (see protocol section 5.3.1)

7.7 Visit 5 - Endocardial EP Ablation Procedure (Day 91-121 post Epicardial Surgical Ablation Procedure)

The Endocardial EP Ablation Procedure (**See Section 5.3**) will be performed between Day 91 – Day 121.

Pre-Endocardial EP Ablation Procedure Subject Assessment: The following baseline data must be conducted and/or obtained prior to starting the Endocardial EP Ablation Procedure:

- Patient AEF Education
- It is required that an acid reducing agent be prescribed 7-days prior to the procedure and continued for a minimum of 30-days post procedure.
- Hospital Admission Date
- Targeted Physical Examination
- Medications Review
- Anticoagulation Testing (e.g., INR for subjects on warfarin (Coumadin) or aPTT or ECT if on dabigatran)
- Weight
- Blood Pressure and Heart Rate
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine, Sodium, Potassium, CO2, Chloride, PT/PTT (within 7 days prior to the procedure)
- Heart Rhythm Assessment - 30 second ECG
- Adverse Event Assessment

The following must be conducted and/or obtained during the Endocardial EP Ablation Procedure:

- TEE
  - Confirmation of LAA exclusion. Images will be sent to a core lab.
  - Presence of thrombus in Left Atrium

  Note: If thrombus is observed in the left atrium per TEE, the EP ablation procedure should be deferred until thrombus is resolved.
- Type of Anesthesia
- EP Procedure Details
- Medications Review
- Post procedure Heart Rhythm Assessment

7.8 Visit 6 – Post Endocardial EP Ablation Procedure

The following must be conducted and/or obtained **within 1 day** post Endocardial EP Ablation Procedure:

- Heart Rhythm Assessment - 30 second ECG

- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Medications Review
- Adverse Event Assessment
- Hospital Discharge Date

7.9 2nd Blanking Period – 90 Days Post Endocardial Ablation Procedure

Blanking Period Arrhythmia Treatment – One additional endocardial procedure will be allowed for any atrial arrhythmia during the 2nd blanking period. The subject may be treated **after** Visit 7 (7 Day Post Endocardial EP Ablation Procedure). The following will be conducted and/or obtained:

- Adverse Event Assessment
- Heart Rhythm Assessment - 30 second ECG
- Medication Review
- Treatment Decision
- If a decision is made to perform an additional endocardial EP ablation procedure during the 2nd blanking period, the following will be obtained:
  - Ablation Details

7.10 Visit 7 – 7 Day Post Endocardial EP Ablation Procedure

A phone call follow-up evaluation will be completed on **day 7 (+ 1 day)** post Endocardial EP Ablation Procedure. The following must be conducted and/or obtained at the 7 Day Visit:

- Health Status
- Medications Review
- Adverse Event Assessment

7.11 Visit 8 – 1 Month Post Endocardial EP Ablation Procedure

A follow-up evaluation will be scheduled for **1 month (30 days + 7 days)** post EP Endocardial Ablation Procedure. The following will be conducted and/or obtained be performed at the 1 Month Visit:

- Targeted Physical Examination
- Weight
- Blood pressure and Heart Rate
- NYHA Class
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Heart Rhythm Assessment - 30 second ECG
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Medications Review Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran)
- Adverse Event Assessment

7.12 Visit 9 – 3 Month Post Endocardial EP Ablation Procedure

A follow-up evaluation will be scheduled for **3 months (90 days + 14 days)** post EP Endocardial Ablation Procedure. The following will be conducted and/or obtained be performed at the 3 Month Visit:

- Targeted Physical Examination
- Weight
- Blood pressure and Heart Rate
- NYHA Class
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Heart Rhythm Assessment - 30 second ECG
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Medication Review
- Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran)
- Adverse Event Assessment
- Begin AAD optimization period if patient is in AF.

7.13 Visit 10 – 6 Month Post Endocardial EP Ablation Procedure

A follow-up evaluation will be scheduled for **6 months (180 days ± 30 days)** post Endocardial EP Ablation Procedure. The following will be conducted and/or obtained at the 6 Month Visit:

- Targeted Physical Examination
- Weight
- Blood pressure and Heart Rate
- NYHA Class
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Heart Rhythm Assessment - 30 second ECG
- 24-Hour Continuous ECG Monitoring/ Arrhythmia Monitoring - Holter or ZioTM Patch
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Medications Review
- Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran)
- Adverse Event Assessment
- Symptom-driven event monitoring will begin at this visit. Subjects will receive a symptom-driven monitor at this visit to capture any symptoms of atrial fibrillation. Site will instruct the subject on use of the monitor along with how to upload data to core laboratory for interpretation of rhythm.
- CT/MR imaging only if subject exhibits symptoms suggestive of pulmonary vein stenosis. (Note: Use same imaging technique performed at baseline PV imaging to the extent possible.)

7.14 Visit 11 – 12 Month Post Endocardial EP Ablation Procedure

A follow-up evaluation will be scheduled for **12 months (365 days + 30 days)** post Endocardial EP ablation procedure. The following will be conducted and/or obtained at the 12 Month Visit:

- AFEQT Questionnaire

- Targeted Physical Examination
- Weight
- Blood Pressure and Heart Rate
- NYHA Class
- RBC, WBC, HGB, HCT, Platelets, BUN (Urea), Creatinine
- Heart Rhythm Assessment – 30 second ECG
- 24-Hour Continuous ECG Monitoring/ Arrhythmia Monitoring - Holter or ZioTM Patch
- Concomitant procedures to treat arrhythmia (i.e., cardioversion for subjects in atrial fibrillation), performed at physician discretion
- Medications Review
- Anticoagulation Testing in accordance with institutional SOC (e.g., INR for subjects on warfarin or aPTT or ECT if on dabigatran)
- Adverse Event Assessment
- Collect symptom driven monitor from subject at this visit and ensure subject's data has been uploaded to core laboratory for rhythm assessment.
- CTA for LAA exclusion (subjects who had AtriClip placed during the Epicardial Surgical Ablation Procedure). Images will be sent to a core lab.
- CTA imaging pulmonary veins should be performed for assessment of pulmonary vein stenosis. Imaging will be sent to a core lab if the subject is symptomatic for PV stenosis.
- (Note: CT/MRI is acceptable method for PV imaging if the subject did not have an AtriClip placed during the Epicardial Surgical Ablation period. In that case, use the same imaging technique performed at baseline PV imaging to the extent possible. If subject cannot tolerate CTA, a TEE is also an acceptable method to assess for LAA exclusion.)

7.15 Visits 12, 13, 14, and 15 (2, 3, 4, and 5 years Post Endocardial EP Ablation Procedure) – Annual Follow-Up Visits

A follow-up evaluation will be scheduled for the **annual follow up visits (± 60 days)**. The following will be conducted and/or obtained at the annual follow up visits:

- Medications Review
- 24-Hour Continuous ECG Monitoring/ Arrhythmia Monitoring - Holter or ZioTM Patch
- Emergency room visits for atrial fibrillation, atrial flutter, and atrial tachycardia
- Hospital re-admission for atrial fibrillation, atrial flutter, and atrial tachycardia
- Incidence of atrial fibrillation, atrial flutter, and atrial tachycardia that require treatment
- Pacemaker implantation
- Additional catheter ablations
- Incidence of DC cardioversion to address Atrial Dysrhythmia
- Incidence of stroke or TIA

7.16 Phone Visits

Contact with the subjects should be attempted at approximately 6 months after each annual visit (approximately 18, 30, 42, and 54 months) to collect:

- Subject status including health status
- Current contact information

7.17 AEF Unscheduled Visit

AEF Unscheduled visit in the event of suspected AEF after Visit 3 or Visit 5. If AEF is suspected, endoscopy and/or TEE probes should be avoided.

- Assessment of AEF symptoms

Note: Hospital Standard of Care will be followed to assess, diagnose and treatment when AEF is suspected. A computed tomography scan is the typical tool used to diagnose AEF. Since a CT scan may be conducted early in the course of AEF diagnosis, a repeat CT image should be considered if the initial CT scan is normal, but symptoms and findings indicative of AEF do not resolve.

7.18 Study Exit

At study exit the following must be collected.

- Study Exit Date
- Exit Reason

7.19 Repeated Study Visit Tests

All study procedures should be conducted at the investigational site. Follow-up testing may be performed at another site only if it is not possible for the subject (or the subject refuses) to return to the investigational site. In such cases, the Investigator may arrange for the study-required testing to be completed by the subject's local physician. However, it remains the responsibility of the study Investigator to ensure collection of appropriate information. Copies of source documents from the local physician must be obtained and kept in the subject's study file.

AEF Education – (Patient Educational Brochure and Patient Emergency Wallet Card)
Patient will be counseled regarding AEF warning signs and treatment. The Patient Educational Brochure and Patient Emergency Wallet Card will be provided to the patient and will be reviewed.

Neurologic Assessment – The Modified Rankin Scale (mRS) should be performed after the NIH Stroke Scale (NIHSS) has been determined and graded. The same individual who performed the NIH Stroke Scale should perform the Modified Rankin Scale (mRS) assessment. Study staff must be trained prior to administration of the scales (NIHSS requires certification).

Targeted Physical Examination – A targeted physical exam (PE) includes an assessment of the following body systems: General Appearance, Cardiovascular, Respiratory, and Musculoskeletal. A more thorough PE may be conducted according to institutional SOC. If any findings are noted during the PE, the finding should be recorded in the source documents as medical history or as an adverse event, as appropriate. The finding shall be recorded in the eCRF as required per the Safety section of the protocol (**Section 10.0**).

Weight, Blood Pressure and Heart Rate – The subject's weight, blood pressure and heart rate will be assessed using the site's SOC.

AFEQT – The AFEQT is a self-administered questionnaire. The completion of the instrument should take about 5 minutes. In the clinic or doctor's office, the AFEQT questionnaire should be administered prior to seeing and/or being examined by the physician to ensure the subjects' responses are not influenced by the physicians' evaluation. If other questionnaires are to be

administered, the AFEQT should be completed first. Subject should be encouraged to answer each question. If the subject asks for clarification of a particular item, read the question to the subject verbatim. If the subject continues to ask for clarification explain to the subject that they should use their own interpretation of the question.

Serum Analysis – A serum sample (fasting not required) will be collected from the subject according to the site's SOC and sent to the institutional local laboratory to assess the parameters required at each Study Visit.

Medications Review – All medications, including vitamins or nutritional supplements currently prescribed to, or taken by, the subject shall be recorded in the subject's source documents. Only medications taken for antiarrhythmic or oral anticoagulation therapy need to be reported on the eCRFs.

Heart Rhythm Assessment - An ECG will be utilized during office visits to obtain a rhythm assessment. During procedures, the hospital SOC will be utilized to obtain the heart rhythm assessment. **A minimum of a 30 second ECG Rhythm Assessment should be performed.** The rhythm strip should be retained with the subject's source documents. The subject's rhythm status will be captured in the eCRF.

Adverse Event Assessment – Refer to **Section 10.0** for description of collection of Adverse Events.

Anticoagulation Testing – Performed in accordance with institutional SOC depending on subject's current anticoagulation therapy. Testing will be recorded subjects source documents only.

Arrhythmia Monitoring – Arrhythmia monitoring (Holter or Zio™ Patch) will be worn by all subjects. Data from the Holter or Zio™ Patch will be submitted to the independent core laboratory for analysis.

Symptom Driven Monitoring – All subjects will have symptom driven AF monitoring collected after the last procedure blanking period through 12 months. A phone call reminder will be provided to subjects reminding to collect any AF symptoms using the provided symptom driven monitor.

Phone Visits – Two attempts will be made to contact a subject. If the subject cannot be contacted after the second attempt, this will be recorded on the eCRF. However, the subject will continue to be enrolled in the study.

CTA/CT/MRI/TTE/TEE – These procedures will be conducted according to the site's institutional SOC. Depending on the parameter being measured or the subject requirements, equivalent or superior diagnostic procedures can be utilized as long as the required data can be adequately obtained and is in the protocol required time window. For example, if CTA cannot be performed (i.e., patient is allergic to contrast media or has poor kidney function), TEE is also acceptable to verify exclusion of the LAA. The PI should document the acceptability of any alternate diagnostic procedures.

LAA Exclusion –An independent imaging laboratory will be utilized for assessment of the complete exclusion of the LAA defined by lack of fluid communication (<3 mm residual

communication with LAA and < 10mm residual pocket) between the LA and LAA confirmed by TEE, CTA or MRI evaluation.

8.0 DATA MANAGEMENT AND INTEGRITY

8.1 Data Completion and Record Keeping

8.1.1 Source Documents

Source documents are documents on which information regarding subjects are first recorded. PI subject files or hospital records generally are the basis of source document information. This may include but is not limited to, original subject files, hospital/clinic records, original recordings/tracing, digital images from automated instruments, X-ray films, and laboratory results.

Source documents must be retained by the PI as part of the subject's permanent medical record. The information in the source documents is used to complete the eCRFs. All information captured on the eCRFs should be completely and accurately supported in source documentation. Study Monitors will verify data reported on eCRFs with site source documents. Any additional information relevant to the study should be included in the source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents. The PI will retain originals of all source documents, subject consent forms, and study data.

8.1.2 Data Collection

An EDC system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application This system was designed and is developed and maintained by Fortress Medical Systems in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The platform software has been validated in accordance with 21 CFR Part 11, European Commission's Directive on Data Protection and US Safe Harbor Certification. Prior to being released for data entry, validation of the study level components (i.e., data entry screens, associated edit checks and workflow) will be conducted in accordance with approved user acceptance testing procedures. Access to this system will be controlled so that only authorized users will have the ability to enter into the system. The system is considered a closed system according to 21 CFR Part 11 Electronic Records: Electronic Signatures.

The EDC system will be used to facilitate the collection of all study data at the site. Designated site personnel will be responsible for entering subject data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function.

An EDC digital User Manual will be available under the help menu within the Clindex® website to assist in the collection and entry of source data into the electronic casebook.
Investigative study sites will be asked to enter subject data into the eCRFs no later than 2 weeks from the time the subject was seen for their scheduled study visit.

Detailed description of the eCRF components are included in the eCRF Completion Instructions. These will be provided to the Investigators prior to initiating subject enrollment. The respective eCRFs must be fully completed for each subject and signed electronically.

The subject-AFEQT will be recorded on paper-based questionnaires. The data will then be entered into the respective eCRF within the electronic data capture system by the Clinical Investigator or designee. The AFEQT measures captured on paper-based questionnaires must be stored in the subject's medical notes, as these will be considered to be the source document.

Any errors on paper forms should be crossed out with a single stroke, initialed and dated. Typing correction fluid must not be used. The Investigator will retain one copy of each completed paper CRF in the medical notes and another copy will be kept in the site study file.

Data collected during the clinical investigation for each subject will be maintained as accurately and completely as possible with entries into an electronic data capture system provided by AtriCure. The personal data recorded on all documents, including copy documents, and within the system will be regarded as confidential. The Investigator will be responsible for the timing, completeness and accuracy of the details entered within the electronic data capture system. All data entered in the database must have source documents in the subject's medical records.

Data will be entered into the electronic data capture system by members of the Investigational team who have received training in the use of the system. The system will generate data queries at the point of data entry based on validation checks defined by AtriCure. Such validation checks will primarily be focused on validation of key variables including selected subject demographics, appropriate value ranges and date checks. Resolution of the queries will be the responsibility of the Clinical Investigator and investigation team members. Following completion of all data queries on each eCRF, the Clinical Investigator will be responsible for reviewing and confirming agreement to the data within the system.

The Investigator must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the Investigator must keep a separate list of all subjects entered into this clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes). A Subject Identification Log will be provided in the Investigator's File for this purpose.

8.1.3 Data Correction

Corrections to eCRFs will be prompted via automated electronic edit checks and queries manually created by reviewers. The corrections and the individual making the correction(s) to the eCRF will be within Clindex.

8.1.4 Investigator Regulatory Binder

Each Investigator must maintain an accurate, complete, and current copy of the Regulatory Binder. Upon receipt of copies of changes or revision updates to the Binder from the Sponsor, the Investigator will add the updated document to the Regulatory Binder and will mark the outdated portion of the Binder as "obsolete" by crossing a diagonal line across the page(s) along with date the page was made obsolete and the initials of the person performing the update. The outdated pages will be removed from their current section and filed in the "Protocol Amendment" section along with the Revision Log provided by the Sponsor. If an Investigator holds multiple copies of the Regulatory Binder, then all copies must be updated with the current revisions.

8.1.5 Study Correspondence

Each Investigator and all personnel from the investigational site will maintain records of all

correspondence, electronic, written, and consent, relating to any aspect of the clinical investigation. The records are maintained in the Investigator's Study Binder consisting of, but not limited to correspondence with other participating clinical investigators, the reviewing IRB, and the Sponsor. The Study Monitor will examine the contents of the correspondence.

8.1.6 Data Privacy

Subjects will be made aware that their personal data will be collected and processed in accordance with data protection legislation including the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subjects will be asked to sign an Authorization for Release of Personal Health Information (PHI) for the purpose of this investigation. This authorization may be combined with the ICF depending on local IRB preference. Results from the Clinical Investigation may be published. However, Subject confidentiality will be maintained at all times and it will not be possible to identify individual Subjects from any data presented.

Investigation Sites Outside of the US, Confidentiality will be maintained in accordance with provisions of the 1998 UK Data Protection Act or national transposition of the EU Data Protection Directive 95/46/EC or local equivalent legislation. Data protection consent will be obtained from the subjects as part of the informed consent process. Where applicable data protection submissions will be performed.

8.1.7 Record Retention, Inspection, and Custody

The PI must maintain all documentation related to the study until notified by the Sponsor. The PI will allow representatives of the Sponsor, IRB/EC, the FDA, or other government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Subject medical records will be maintained in a confidential manner. Study reports will not identify subjects by name. These reports may be submitted to the FDA and/or regulatory authorities.

If custody of the records is transferred, notice of such a transfer should be given to the Sponsor no later than ten (10) working days after the transfer occurs.

The Investigator should retain copies of all documents pertaining to this clinical investigation (including source documentation, the informed consent document and any other documents to identify the subjects) for at least 2 years after this clinical investigation is completed. In addition, if the Clinical Investigator moves/retires, etc., he/she should provide AtriCure Inc. the name and address of the person who will look after and be responsible for the subjects' clinical investigation related records.

8.1.8 Medical Dictionary Coding

Medical dictionary coding will be performed using a coding thesaurus algorithm. The MedDRA will be used upon data entry and query resolution for AEs, SAEs, via automated and manual coding processes.

8.1.9 Data Quality Assurance

Quality control and quality assurance processes implemented during this study to ensure subject safety rights, and welfare are protected and to foster data integrity are characterized below.

8.1.10 Investigator Training

Protocol Specific Training

Training will be scheduled once IRB approval is obtained, and the Clinical Study Agreement is executed.

The training of clinical site personnel will be the responsibility of AtriCure, Inc. This procedure may only be performed by qualified investigators, familiar with the study procedures and techniques. A formal training program consisting of didactic and interactive sessions will be performed at each investigational site with participating investigators and study personnel identified at each site prior to subject enrollment. This **Investigator Training Plan** is described in **Appendix 3**.

The Investigator and the study staff will also be trained in general aspects of the procedure, study administration, content and manner of administration of the questionnaires, all procedures in the protocol, and the procedure for electronic data acquisition and transmission. Site personnel will be trained on the study protocol by the Sponsor through a combination of teleconferences, Web-Ex conferences and on-Site training, as appropriate. Training will be documented. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this study are trained.

8.1.11 Monitoring

This study will be monitored by the sponsor to ensure:

- The rights and well-being of the subjects are protected;
- The reported study data is accurate, complete, and verifiable from source documents; and
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), applicable GCPs, and with applicable local/regional regulatory requirements.

AtriCure, as Sponsor of this study, will be responsible for monitoring this study. The monitor's duties are to aid the Principal Investigator in the production and maintenance of complete, legible, well-organized and easily retrievable data. In addition, the monitor will be responsible for assuring the Principal Investigator understands the protocol and all applicable regulations. Approaches to monitoring include on-site visits and may include a remote visit, as appropriate and the rationale and frequency for monitoring will be at the Sponsor's discretion. The extent and nature of monitoring will be predetermined and based on considerations such as the objective, design, complexity, and endpoints of the study and mutually agreed to by the Sponsor. The frequency of monitoring will be determined for each site based on factors including: the planned enrollment, the rate of enrollment, and the current study conduct. Study conduct can be evaluated remotely based on compliance percentage, discrepancy rate and discrepancy type. Monitors will be trained on and comply with established standard operating procedures as well as a written monitoring plan specified by the Sponsor.

In order to perform the monitoring role effectively, the monitor must verify eCRF entries with source documents. The monitor must be given access to primary subject data which supports

the information recorded on the eCRF, i.e., hospital notes, appointment books, original laboratory records, etc. Access to these documents must also be given should the regulatory authority in the instance of an external inspection. Since a subject has the right to refuse access to these documents on the grounds of confidentiality, consent to access is included in the informed consent document, which the subject signs.

The Principal Investigator will receive reasonable notification prior to each monitoring visit during the course of this clinical investigation. The Principal Investigator will be expected to co-operate with the monitor at each visit for the review and verification of eCRFs and any additional records that may have been previously arranged between the Principal Investigator and the monitor.

8.2 Changes to Protocol, Protocol Deviations and Protocol Amendments

8.2.1 Changes to Protocol

The Investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In the event of an emergency situation, the Investigator must notify the Monitor or AtriCure immediately. A full written report of the situation must be forwarded to the IRB/Ethics Committee who approved the original protocol and AtriCure within 10 working days of the event.

8.2.2 Protocol Deviations

The Investigator agrees to conduct the study in accordance with this protocol; however, protocol deviations may occur during the course of the study. Protocol deviations are events occurring during the conduct of the study which are not in compliance with the protocol and for which an amendment has not been granted. Protocol deviations can be committed by the Sponsor, the PI, or study subject. A deviation can be identified from a number of sources. Potential sources include but are not limited to a member of the PI's staff, the monitor during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. The PI or PI's representative are encouraged to contact the monitor or AtriCure as soon as possible upon observing a protocol deviation. Regardless of the source, it is crucial to document the deviation and record all corrective actions. Protocol deviations will be reported in the final report.

The process for capturing deviations will be detailed in the monitoring plan. The process will require that documentation describe the deviation, appropriate actions taken, and will be included in the study file for the respective PI and subject. The study site representative will be advised to record the deviation and relevant discussion with the Sponsor about the deviation in subject source documents.

Protocol deviations affecting the scientific soundness of the study or the rights, safety, or welfare of the subjects, will be reported by the PI, as required by the IRB/EC.
Protocol deviations will be summarized and grouped into relevant categories for analysis and may include, but not be limited to, subjects who:

- Entered the study although they did not satisfy the eligibility criteria; or
- Developed withdrawal criteria during the study, but not removed.

8.2.3 Protocol Amendments

If it becomes necessary to amend the protocol, then the nature of the amendment will be agreed between the Sponsor and the Principal Investigator(s) and this will be recorded with a justification for the amendment. The appropriate IRBs/EC will be informed of amendments prior to implementation of the change.

9.0 STATISTICAL METHODS

9.1 Clinical Study Objective

The objective of this study is to evaluate the effectiveness and safety of minimally invasive cardiac surgical ablation utilizing the AtriCure Bipolar System and AtriClip PRO LAA Exclusion System in a Dual Epicardial and Endocardial Procedure (DEEP) for the treatment of persistent or longstanding persistent AF. It is expected that this combined technology will provide a substantial increase in effectiveness over the current treatment options, with only a moderate increase in safety risk.

9.2 Primary Endpoints

9.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds in duration (or for the entire length of a 30-second ECG tracing) through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). Any arrhythmia that occurs within the blanking period or during the AAD optimization period, prior to the 6-month visit will not be considered a failure. The rhythm status used for evaluation of this endpoint shall be derived regularly scheduled monitoring as well as any symptom driven monitoring that is performed. For the purposes of this study, atrioventricular nodal reentrant tachycardia (AVNRT), inappropriate sinus tachycardia, and Wolff–Parkinson–White syndrome (WPW) will not be considered procedure failures.

The 12-month follow-up window utilized for this endpoint is based on time from the catheter ablation procedure. However, if a subject refuses the second stage of the DEEP procedure, i.e., the catheter ablation procedure, or experiences a safety event or medical condition precluding the catheter ablation procedure, every attempt will be made to continue collecting follow-up data, including their primary effectiveness status at 12 months after the surgical procedure (the 3-month blanking and AAD optimization periods measured from the surgical ablation procedure in this case). If their status cannot be ascertained, the endpoint will be missing, and thus subject to missing value methods below.

9.2.2 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint consisting of any one or more of the following events if they are adjudicated by the CEC to be serious adverse events (SAEs) and related to device/procedures as follows:

1. AtriCure Bipolar System, AtriClip Pro LAA Exclusion System, within 30 days of the epicardial surgical ablation procedure; or

2. The epicardial surgical ablation procedure within 30 days following the epicardial procedure; or
3. The endocardial index procedure (or a repeat endocardial ablation procedure performed during the blanking period) within 7 days following an endocardial ablation procedure

Events except as otherwise specified for a particular condition include:

a. death (regardless of cause)
b. stroke
c. transient ischemic attack (TIA)
d. myocardial infarction (MI)
e. pulmonary or systemic embolism
f. pericarditis resulting in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires a new hospitalization, or persists for more than 30 days following the ablation procedure
g. excessive bleeding, defined as one or more of the following:
    i. re-operation to control bleeding within 7 days post-epicardial surgical procedure or surgery to control bleeding within 7 days post-endocardial ablation procedure, if related to an AtriCure device or to the procedure;
    ii. receipt of ≥ 2 units of blood transfused in a 24-hour period during the first 7 days post epicardial surgical procedure or within the first 7 days post-endocardial ablation procedure, if related to the device or procedure;
    iii. conversion to sternotomy or thoracotomy that requires ≥ 2 units blood to be transfused or that is triggered by hypotension, cardiac arrest, or repair of a cardiac injury
h. wound infection at surgical site requiring re-operation for wound debridement
i. atrio-esophageal fistula (from the time of surgical procedure through 12-month follow-up visit)
j. permanent phrenic nerve paralysis, defined as paralysis that remains unresolved at the 12-month follow-up visit
k. permanent pacemaker implantation that is a direct result of injury to the specialized conduction system (SA node or AV node) during the epicardial surgical ablation procedure
l. pulmonary vein (PV) Stenosis of >70%, as measured at any time after the catheter ablation procedure through the 12-month follow-up visit
m. major vascular access complications, including development of a hematoma, an arteriovenous fistula, or pseudoaneurysm that requires surgical intervention or transfusion, or that prolong hospital stay, or require a new hospital admission

9.3 Sample Size and Power

This study is powered for the primary effectiveness and primary safety endpoints. Both of these endpoints are compared to objective performance criteria, as a single-arm study has been determined to be the least burdensome and most appropriate approach. As with the FDA heart valve guidance document [20], this is justified by the extensive reporting in the literature of treatment outcomes for AF. Though catheter ablation would be the most natural comparison, no catheter ablation device has yet been approved for the persistent or longstanding persistent AF population. It is known that the rates of long-term effectiveness after catheter ablation in persistent and long-standing persistent AF patients are lower than in paroxysmal AF patients [21]. Similarly, adverse device effect (ADE) rates are likely higher in persistent populations due to the fact that these patients tend to be older, have longer AF history, and have more congestive heart failure than paroxysmal populations[22]. Thus, studies reporting results for aggregated AF populations tend to

be more favorable than what is seen in strictly persistent populations.

Based on the premises delineated above, the sample size calculations for powering the two primary endpoints are given in the following sections.

Effectiveness

The 12-month effectiveness rates after various dual/hybrid surgical epicardial procedures reported in the published literature vary widely, as most are from single center studies with varying procedural techniques and varying degrees of rhythm monitoring[23, 24, 25, 26, 27, 28, 29]. Some sites reported on surgical-only procedures, others on concomitant epicardial/endocardial procedures, staged 2-part procedures, and combinations of these designs. Based on a detailed review of this literature and the two feasibility studies performed with the AtriCure Bipolar System, the lead investigators for this study believe that a 70% effectiveness rate after 12 months of follow-up is a reasonable estimate for the primary success endpoint.

While estimates of effectiveness success after catheter ablation also vary widely, primarily due to length of follow-up, severity of AF, and the definition of failure utilized, the overall success in a persistent population at 12 months, as defined by current guidelines, is believed to be less than 60%. In particular, the only regulatory trial for catheter ablation of atrial fibrillation with posted trial results, the Medtronic Ablation Frontiers TTOP trial, which utilized a similar population with a less stringent endpoint of a 90% reduction in AF after only 6 months of follow-up 3 months beyond the blanking period), had a success rate of 55.8% [30, 31, 32]. A recent study in Spain (SARA) reported that 60.2% (59 of 98) of persistent AF patients (where LS persistent patients were excluded) were free of any recurrence of >30 s at 12 months follow-up[33]. A report of 5-year outcomes in a LS persistent AF population of 202 patients showed that 35% remained in SR at 1 year after a single catheter ablation and 58% remained in SR at 1 year after multiple procedures, with persistent AF duration a highly significant predictor of relapse[34].

Based on a thorough review of the literature, an OPC of 60% success was chosen as the acceptable lower confidence limit for effectiveness in the combined persistent and LS persistent populations of this study. Thus, the goal for the primary effectiveness endpoint is to establish that the DEEP procedure significantly increases effectiveness relative to an OPC of a 60% catheter ablation success rate. Using the expected effectiveness success rate of 70% for the DEEP procedure, a one-sided alpha=0.025 level of significance, and a normal approximation to the binomial distribution with continuity correction, a sample size of N=182 is required to ensure 80% power.

Safety

Due to the groundbreaking new procedure that will be utilized in this trial, there are no regulatory trials with reported safety results for any type of similar minimally invasive procedure. The published literature for similar procedures is sparse and safety events are not reported with any consistency. Thus, the only realistic estimate of safety event rates is derived from the most recent feasibility trial. Based on this trial, a best estimate of the primary safety event rate over the dual procedures is 19%.

Patients with persistent AF are at increased risk of ischemic stroke and heart failure, while they may also be at increased risk of hemorrhagic stroke due to oral anticoagulation. In addition, their quality of life and ability of work can be greatly affected by both the disease and by the medications

used to treat the disease. All of the patients in this study will have tried and failed at least one treatment and many have failed several treatments, whether multiple AADs or AADs and catheter ablation.

The patients themselves and their treating physicians are willing to tolerate a substantial level of risk, if the reward is a similarly substantial level of benefit. The tolerable risk level, from the perspective of both the patients and the treating physicians, is related more to the subset of events that would cause permanent damage (i.e., death, stroke, MI, permanent and significant phrenic nerve damage) than to the overall level of procedure-related SAEs. It is believed that the rate of this subset of events will be quite low in the proposed study and that the benefit to the patient in terms of AF reduction or resolution, substantially reduced stroke risk, heart failure risk, and bleeding risk, and a substantial increase in quality of life will be the expected benefits.
There have been no regulated trials in this persistent AF population for a treatment that has produced the magnitude of benefit expected in this trial, and thus there is no comparable published standard for acceptable risk in relation to benefit. Rather, the acceptable risk level is proportionate to a patient's current risk profile and quality of life, based on their AF, and the anticipated level of benefit from the proposed treatment.

For these reasons, the clinicians involved in this study have agreed that a 28% rate of safety events, as specifically defined in the primary safety endpoint, and with the expected mix of permanent vs. resolvable events, is an acceptable risk level in relation to the expected benefits of this treatment.

In order to have an 80% chance of showing that the DEEP procedure has a primary safety event rate of <28% (UCL) when the actual underlying rate is 19%, a sample size of N=192 subjects is required. This sample size calculation is based on a one-sided α=0.025 level of significance and assumes a normal approximation to the binomial distribution with continuity correction.

Overall Sample Size
The primary effectiveness and safety endpoints require similar numbers of patients, with the effectiveness endpoint driving the overall sample size. Due to the potential for significant loss to follow-up prior to the primary effectiveness endpoint at 12 months. In order to allow for an attrition rate of approximately 20%, this study will treat up to 220 subjects.

9.4 Randomization

Randomization is not applicable, as this is a single arm study design.

9.5 Analysis Populations

The following analysis populations are defined for utilization in the data analysis:

- **Intent to treat patient population (ITT):** The ITT subject population will include all enrolled subjects who have met all inclusion/exclusion criteria.
- **Safety Population**: The safety population will include all enrolled subjects that undergo induction of anesthesia.
- **Per protocol patient population (PP):** The PP patient population will include all subjects who complete both the Epicardial Surgical Ablation Procedure and Endocardial EP Ablation Procedure.

- **AtriClip Effectiveness population:** The AtriClip effectiveness population will include all ITT subjects for whom an attempt (entrance of the AtriClip into the chest wall) is made to place an AtriClip device.

The primary effectiveness analysis will utilize the ITT patient population. Secondary effectiveness analyses will be conducted on the ITT and the PP patient populations. All safety analyses will utilize the safety population.

9.6 Secondary Endpoints

9.6.1 Secondary Endpoints – Effectiveness

For labeling purposes, to be tested if the primary effectiveness endpoint is a success:

1. Exclusion of the LAA, defined as defined by lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA. This endpoint will be measured at the 12-Month (Visit 11) (approximately 15 months post AtriClip placement). The AtriClip effectiveness population will be utilized for analysis of this endpoint.

   Based on a literature review of peer-reviewed research that was performed for the EXCLUDE trial (add reference here for the trial), a weighted average rate of 77.5% exclusion at 3 months was derived as a reasonable expectation of success, based on a combination of cut and sew and stapling procedures[35-44]. That same trial resulted in actual exclusion rates of 95.7% (67/70) for intra-procedural success and 98.4% (60/61) for 3-month success. Utilizing the most conservative of these results gives a 95% lower confidence limit of just under 88% for an exact binomial confidence interval.

   In the current study, it is believed that the placement of a clip will provide a significant benefit to the patient with extremely low added safety risk. A success rate of over 80% will exceed the 77.5% expectation of success based on other exclusion methods, with less risk of injury than those methods[35-44], and is a reasonable expectation based on the EXCLUDE results that showed a lower bound of just under 88%. The associated hypothesis test, based on an exact binomial confidence interval, will be as follows:

$$H_o : p_2 \leq .80 \quad vs. \quad H_a : p_2 > .80$$

Exploratory endpoints:

2. Exclusion of the LAA, defined as lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA. The endpoint will be measured intra-procedurally (Visit 2), and at the Endocardial EP Ablation Procedure (Visit 5). The AtriClip effectiveness population will be utilized for analysis of this endpoint.
3. Acute procedural success of surgical epicardial procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins, as well as the “box”. The ITT and PP populations will be utilized for analysis of this endpoint.
4. Acute procedural success of endocardial catheter procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins and the “box”, as well as bi-directional block of the cavo-tricuspid isthmus. The ITT and PP populations will be utilized for analysis of this endpoint.
5. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter without AAD, defined as no documented event >30 seconds in duration (or for the entire length of an ECG tracing) with no utilization of AADs beyond the blanking and AAD optimization period, except as previously failed without an increase in dose. This endpoint will be measured through the 12-month, 2-, 3-, 4-, and 5-year visits (Visits 11-15) via cumulative ECG monitoring. The ITT and PP populations will be utilized for analysis of this endpoint.

6. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter regardless of AAD, defined as no documented event >30 seconds in duration (or for the entire length of the ECG tracing) regardless of AAD usage. This endpoint will be measured through the12 month, 2-, 3-, 4-, and 5-year visits (Visits 11-15) via cumulative ECG monitoring. The ITT and PP populations will be utilized for analysis of this endpoint.
7. Freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >10 minutes duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). The ITT and PP populations will be utilized for analysis of this endpoint.
8. Change in Quality of Life, defined as the total AFEQT score measured at the 12-month follow-up visit minus the score at the baseline visit. The score will be calculated per the AFEQT scoring manual. The ITT and PP populations will be utilized for analysis of this endpoint.

9.6.2 Secondary Endpoints – Safety

All secondary safety endpoints are supplemental and intended to provide a more complete picture of the overall safety profile for the DEEP procedure. They will not be tested for labeling purposes.

1. Major surgical events – This will be a composite safety endpoint within 30 days of epicardial surgical procedure, as otherwise defined in the primary safety endpoint.
2. Major catheter events – This will be a composite safety endpoint within 7 days of endocardial catheter procedure, as otherwise defined in the primary safety endpoint.
3. 30-day surgical SAEs - This will include all SAEs that occur within 30 days of the epicardial surgical procedure and that are adjudicated to be related to the device or to the procedure.
4. 12-month DEEP SAEs - This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure.
5. Unresolved SAEs – This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure and that are not fully resolved by the 12-month visit. These events shall include any procedure-related deaths, strokes with residual disability, unresolved phrenic nerve damage, or other such events that are adjudicated to have resulted in chronic disability or permanent damage.
6. Any serious adverse event through the 12-month follow-up visit, regardless of attribution.
7. Incidence of stroke or TIA at 12, 24, 36, 48, 60-month visits. The ITT population and the AtriClip effectiveness population will be utilized for analysis of this endpoint.
8. Any esophageal injury that meets all of the following criteria: identified post epicardial ablation, adjudicated by core lab to be a thermal injury with perforation, and related to an AtriCure ablation device, through 30-days post epicardial procedure.

9.6.3 Secondary Endpoints – Health Economics

All health economic endpoints are exploratory in nature.

1. Utilization of cardioversion, defined as the number of cardioversion events (visits) that a subject had in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.
2. Hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the number of readmissions in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.
3. Total length of stay for all hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the sum of the length of stay for each such visit within the last 12-month period.

This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.

4. Emergency Room Visits for AF, atrial flutter, or atrial tachycardia, defined as the number of visits in the past 12-month period. This endpoint will be measured at the 12-month, 2-, 3-, 4-, and 5-year (Visits 11-15) follow-up visits.

9.7 Analysis of Primary Endpoints

The study will be considered successful if both the primary safety and primary effectiveness endpoints are statistically significant at the 0.025 level (one-sided).

9.7.1 Primary Analyses

Primary Safety

The statistical analysis of the primary safety endpoint will consist of a comparison of the proportion of patients who fail to complete the trial without a primary safety endpoint event to a historical control rate that is based on results from the feasibility trials. Adverse events will be adjudicated in accordance with section 12.1. The proportion of primary safety failures will be calculated with subjects as the experimental unit (i.e., the subject will be considered a failure if a primary safety event was experienced within the timeframes defined in the endpoint). The numerator of the proportion will be the number of subjects who have a primary safety event, and the denominator will be the total number of subjects.

A normal approximation to the binomial distribution, Z-test will be conducted at a one-sided α=0.025 level of significance to test the following hypothesis that the proportion of failures is significantly lower than the OPC:

$$H_o : p_S \geq 0.28 \quad vs. \quad H_a : p_s < 0.28$$

where p_s = the proportion of primary safety failures in the safety population. The safety population will be the primary population for this analysis. Missing values will be treated as described in the Missing Values section below.

Primary Effectiveness

The statistical analysis of the primary effectiveness endpoint will consist of a comparison of the proportion of patients who remain a primary effectiveness success at the 12-month visit to a historical control rate that is based on results from the feasibility trials and published literature. The proportion of primary effectiveness successes will be calculated with subjects as the experimental unit (i.e., the subject will be considered a success if no primary effectiveness failure was recorded from the 6-month visit through the 12-month visit). The numerator of the proportion will be the number of subjects who are a primary effectiveness success, and the denominator will be the total number of subjects.

An exact, one-sample binomial test will be conducted at a one-sided α=0.025 level of significance to test the following hypothesis that the proportion of effectiveness successes is significantly higher than the OPC:

$$H_o : p_E \leq .60 \quad vs. \quad H_a : p_E > .60$$

where p_E = the proportion of primary effectiveness successes. The ITT population will be the primary population for this analysis and the LOCF method will be the primary missing value method, as described in the Missing Values section below.

9.7.2 Secondary Analyses

All secondary statistical analyses of primary endpoints will be exploratory. All analyses will be conducted using appropriate statistical methods as described in the Statistical Analysis Plan (SAP) for the study. These will include analyses of the populations and subgroups as specified in this protocol and may also include additional populations and/or subgroups.

9.8 Analysis of Secondary Endpoints

An exact, one-sample binomial test will be conducted at a one-sided α=0.025 level of significance to test the following hypothesis that the proportion of subjects in the AtriClip effectiveness population with LAA exclusion at the 12-Month Visit (15 months post AtriClip placement) is significantly higher than 80%:

$$H_o : p_2 \leq .80 \quad vs. \quad H_a : p_2 > .80$$

The last observation carried forward (LOCF) method will be utilized for patients who do not have TEE testing at the 12-Month Visit. This method is considered conservative based on the EXCLUDE study[35], which showed a higher exclusion rate at 3 months than at the time of clip placement (98.4% vs. 95.7%).

The remaining secondary endpoints will be exploratory and as such, the data will be tabulated without formal statistical testing.

9.9 Missing Endpoints

All safety analysis will utilize the safety population and no missing values will be imputed unless a subject misses a follow-up visit and cannot subsequently be contacted to determine their primary safety status. In this case, the primary safety endpoint will be considered a failure and the subject will be excluded from any subsequent secondary safety analyses for which their status is unknown. If a procedure is aborted due to a primary safety event, the subject will be considered a safety failure. If a subject misses a follow up visit, but it can be subsequently verified that the subject did not incur a safety failure, the subject will be considered a success.

The primary effectiveness analysis will utilize the ITT population and the LOCF method for missing values, as defined below. A subject with any primary effectiveness failure from the 6-month visit through the 12-month visit will be considered a failure for all methods below. Any subjects who withdraw or are lost-to-follow-up prior to the 12-month follow-up visit, or for any reason do not have 12-month ECG readings available, will be analyzed as follows:

1) **Last observation carried forward (LOCF):** Any subject who is missing a scheduled testing will be considered an effectiveness success or failure at that scheduled visit based on their status up to and including their last testing.
2) ***Worst case:*** Any subject with no primary effectiveness failure recorded and with no 12-month test data will be considered a failure.
3) ***Best case:*** Any subject with no primary effectiveness failure recorded and with no 12-month test data will be considered a success.
4) ***Break-even***: If the study endpoint is met using the best-case methodology and is not met using the worst-case methodology, a break-even analysis will be performed to determine the number of subjects with missing endpoint data who would be required to be a success in order

to meet the endpoint.

All secondary endpoints for LAA exclusion will utilize the LOCF method for missing values. No missing values will be imputed for the remaining secondary endpoints. If a subject is missing a value for one of these secondary endpoints, they will not be included in the analysis of that endpoint. The number of patients with non-missing values will be reported for each endpoint.

9.10 Site and Subgroup Heterogeneity

Primary safety and effectiveness endpoints will be reported by site, by gender, and by classification of persistent AF (longstanding vs. non-longstanding). In addition, logistic regression models will be utilized to test for statistically significant differences in the endpoints due to site regions (US and OUS), gender, and classification of persistent AF (longstanding vs. non-longstanding), while also adjusting for age, BMI, baseline comorbid conditions, LVEF, total length of AF, and number of previous catheter ablations. P-values will be reported for each covariate and odds ratios with 95% confidence intervals will be reported for gender and for classification of persistent AF.

This overall goal of this study is to show safety and effectiveness in a representative population of patients with persistent atrial fibrillation and thus it is not powered for separate analysis of individual subpopulations.

10.0 ADVERSE EVENTS

RF ablation using bipolar energy applied epicardially has been used in concomitant procedures for the treatment of AF for over 10 years and the risks are well understood. More recently standalone (or sole therapy) surgical ablation for treatment of atrial fibrillation has been reported by various institutions to be safe, and with varying degrees of effectiveness (depending on the lesion set, procedure, and subject population). Risks and benefits to the subjects are described in the **Clinical Risk/Benefit Analysis** (**Appendix 4**). **Adverse Event Definitions** are found in **Appendix 5**.

10.1 Definitions

Adverse Event:
Adverse Event (AE): any undesirable clinical occurrence or change from patient's baseline (or pre-device procedure) condition, whether it is considered device related or not.
Adverse Event Identification: a condition that is one of the following:

a) A unique symptom or event that is a change from the subject's baseline status
b) A series of symptoms or events that can be categorized as a single entity based on definitions found herein
c) A specific diagnosis responsible for a clinical change
d) A worsening or exacerbation of a pre-existing condition

Serious Adverse Event:
Serious Adverse Event (SAE): any adverse event is considered serious if it results in death, is life threatening, requires hospitalization (initial or prolonged), results in disability or permanent damage, causes congenital anomaly/birth defect, requires intervention to prevent impairment or

damage, or other serious (important medical events) which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

Note: “Death” should not be reported as an adverse event. The cause of death should be reported as an adverse event. The only exception is “Sudden Death” when the cause is unknown.

Unanticipated Adverse Device Effect (UADE):
Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [21 CFR part 812.3(s)].

Pre-existing Condition vs. Adverse Event:
A pre-existing condition is defined as a medical condition that is present before treatment (treatment being defined as induction of anesthesia) and is to be reported as part of the subject’s medical history. It must be reported as a new AE if the intensity, frequency, or the character of the condition worsens during the study treatment and the AE was determined to have the relationship to the study procedures and/or study devices.

To avoid confusing pre-existing conditions with AEs during data analysis, the study sites must make all attempts to provide start dates for all baseline medical conditions. Any pre-existing condition that now meets the stated criteria as an AE should be recorded on the AE eCRF as an exacerbation of the pre-existing condition and the start date will be recorded as the time when the exacerbation occurred.

10.2 Events Expected to Occur with Epicardial Surgical Ablation Procedure and the Endocardial EP Ablation Procedure

For purposes of this study, the following events are not considered reportable (recorded on eCRF) because they are normally expected to occur in conjunction with treatment for persistent or longstanding persistent atrial fibrillation, atrial fibrillation procedures, or are associated with customary, standard care of patients undergoing minimally invasive cardiac surgery or catheter ablation procedures.

- Chest pain without associated enzyme/ECG changes
- Post-operative pain/post-procedure pain
- Post-anesthesia emesis, nausea, or headache (within 48 hours of procedure)
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction
- 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/post-procedure hematocrit decrease from baseline measured in the OR, prior to the first incision, not associated with hemodynamic changes, remaining above 25% and requiring < 2 units PRBC’s

- Minor, localized tenderness, swelling, induration, oozing, etc. at surgical site or catheter insertion site
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- 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 – Note: this event is expected for surgical procedure only
- 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 mg/dl during the first 48 hours post op does not constitute hyperglycemia
- Pleural effusion unless treatment with thoracentesis or chest tube insertion is required – Note: this event is expected for surgical procedure only
- Pericardial effusion without hemodynamic compromise or treatment
- Atrial Fibrillation / Atrial Flutter / Atrial Tachycardia with or without cardioversion
- Junctional Rhythm requiring temporary pacing

  Note: Subjects will undergo general anesthesia and therefore will also be subject to general anesthesia-associated complications and morbidity. These are also not considered reportable (recorded on eCRF) adverse events.
- Pre-planned Surgical Procedures

Any pre-planned surgical procedures at the time of informed consent will not be considered reportable (recorded on eCRF) (whether hospitalization is required or not). Any blood transfusions during preplanned operative procedure are not considered reportable adverse events.

Note: This listing of events is intended to provide guidance to the Investigator / investigational site for the purpose of adverse event reporting. The Investigator should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above events should be reported as adverse events.

10.3 Adverse Event Classification

The Investigator is required to provide:

- Time interval of the event;
- Date of event onset and outcome of the event, or date of death;
- Severity of the event;
- Action taken for the medical management of the event;
- Relationship of the event; and
- Indication of whether the event is serious.

Time Interval of Adverse Event

The time interval of the occurrence of the adverse should be assessed in relationship to timing of the Epicardial Surgical Ablation Procedure or the Endocardial EP Ablation Procedure.

Severity of Adverse Events

The intensity of an AE should be assessed. A change in severity may constitute a new reportable AE. The following guideline should be used to determine the severity of each adverse event:

- **MILD:** Awareness of experience, but easily tolerated. No medical intervention required.

- **MODERATE:** Enough discomfort to interfere with usual activities. Medical intervention required.
- **SEVERE:** Inability to carry out usual activities. Medical intervention (including hospitalization or prolongation of hospitalization) required.

10.4 Relationship of Adverse Events

It is the PIs responsibility to assess the relationship of an AE. Adverse events will be assigned an attribution according to the Investigator's best judgement of primary cause. Events will be categorized by relationship to the investigational devices (ASU2, ASU3, ASB2, EMR2, EML2, MAX5, MCR1, MLP1), or the AtriClip (PRO1 or PRO2), procedure [ablation procedure (epicardial or endocardial) or general cardiac surgical procedure, subsequent intervention], concomitant medications, pre-existing condition, intercurrent condition, intercurrent intervention, or unknown.

Device Related Adverse Event: An adverse event, which in the judgment of the Investigator, results from use of the AtriCure Bipolar System, the AtriClip or the endocardial ablation devices.

Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the procedure (epicardial surgical procedure or endocardial EP procedure or general cardiac surgical procedure, subsequent intervention) and is not specifically related to the use of the AtriCure Bipolar System.

Concomitant Medication-Related Adverse Event: An adverse event is considered to be concomitant medication related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g. bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: An adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the investigational device, ablation procedure, or general cardiac surgical procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device-, ablation procedure-, or general cardiac surgical procedure-related.

Intercurrent Condition: It is reasonable to believe that the event is directly associated with an intercurrent condition/co-morbidity.

Intercurrent Intervention: It is reasonable to believe that the event is directly associated with an intercurrent intervention which was performed for reasons other than to address a device or ablation/general cardiac surgical procedure related complication.

Unknown – A clinical event (including abnormal laboratory result) that cannot be determined to be related or unrelated to Investigational devices/procedure/drug given information.Reasonable justification need to be provided.

The following definition should be used in determining the relationship of an adverse event:

- **Related** – A clinical event (including abnormal result) that presents a known or suspected relationship between the following categories and the event.
  - investigational devices (ASU2, ASU3, ASB2, EMR2, EML2, MAX5, MCR1, MLP1), or the AtriClip (PRO1 or PRO2);
  - procedure (ablation procedure, epicardial or endocardial) or general cardiac surgical procedure, or subsequent intervention
  - concomitant medications, pre-existing condition, intercurrent condition, intercurrent intervention, or other.

10.5 Reporting Procedures For Adverse Events

10.5.1 General Reporting Requirements - Non-Serious Adverse Events

The Investigator (or designee) will record **all** AEs (both serious and non-serious and regardless of relationship) in the source documents. AEs will be reported on the eCRF (except those in Section 10.2 as described) from the time of treatment (induction of anesthesia) through Visit 11. Only the AEs listed to be collected (Section 10.5.2) in the annual visits (2–5-year visits) will be reported on the eCRF. Prior to induction of anesthesia , any events will be considered patient medical history. Standard medical terminology should be used when recording AEs. The information as described in 10.3 and 10.4 should be recorded for each AE. The following criteria must also be adhered to by the Investigator:

- Use separate Adverse Event Form to document each series of events.
- The Adverse Event Form must be electronically signed by the Investigator or Co-Investigator (if applicable).
- It is the responsibility of the Investigator to inform their IRB of SAEs as required by their IRB/EC procedures and in conformance with FDA requirements.

*Note: It is the responsibility of the Investigator to inform their IRB of **non**-serious adverse events, as required by their IRB procedures and in conformance with FDA requirements.*

10.5.2 Reporting Requirements – Serious and Unanticipated Adverse Events

Serious and any unanticipated adverse events up to Visit 11 (12 month post endocardial procedure) must be reported by the Investigator (or designee) by submitting the Adverse Event Electronic Case Report Form to the Sponsor, within 10 days of becoming aware of the adverse event. An event determined by the Investigator to be life threatening or to have led to death should be reported within 24 hours.

From subject treatment (induction of anesthesia) through Visit 11 all SAEs are reported except those listed in Section 10.2. After Visit 11 through Visit 15 or Subject Exit, SAEs are reported on the eCRF if they are any of the following: death (regardless of cause), stroke, transient ischemic attack (TIA), myocardial infarction (MI), pulmonary or systemic embolism, permanent pacemaker implantation, device related, procedure related, or UADE.

> *In the event of system outages or technical difficulties, serious and any unanticipated adverse events may be submitted via e-mail to SAEInbox@AtriCure.com. Upon availability of the system or resolution of the technical difficulties, the event will be recorded in the Adverse Event eCRF.*

The Investigator (or designee) shall send a written report including a narrative description of the

serious and/or unanticipated adverse event to AtriCure or their designee within three (3) working days of the initial report. The Investigator should follow all unresolved serious adverse events until the events are resolved, or the subject has exited the study, or the adverse event is otherwise explained.

AtriCure, Inc., or their designee, in cooperation with the Investigator, will assess all serious adverse events considered device-related for potential reportability to the FDA as an Unanticipated Adverse Device Effect (UADE) in accordance with 21 CFR Part 812.46(b). If a UADE determination is made, the Investigator and Sponsor will comply with UADE reporting requirements per 21 CFR Part 812.150. The Sponsor shall report the results of such evaluation to FDA and to all reviewing IRBs/ECs and participating Investigators within ten (10) working days after the Sponsor first receives notice of the UADE. Thereafter the Sponsor shall submit such additional reports concerning the effect as FDA requests. Similarly, the Investigator shall submit to their reviewing IRB a report of any UADE as soon as possible, but in no event later than ten (10) working days (or per local IRB requirements) after the Investigator first learns of the effect. The Investigator (or designee) shall provide documentation of the UADE report/notification sent to their IRB to AtriCure (or designee).

Note: It is also the responsibility of the Investigator to inform their IRB of other SAEs (i.e., non-UADEs) as required by their IRB/EC procedures and in conformance with FDA requirements.

- If the subject reports any adverse events that are potentially serious during the follow-up evaluation period, the subject should return to the investigator's facility for further evaluation of the event.

  Note: If the subject exhibits symptoms suggestive of pulmonary vein stenosis, CT/MR imaging should be performed.

10.5.3 Subject Death and Atrio-esophageal Fistula

The investigator (or designee) must report any reported death (determined to be device or procedure related) and/or atrio-esophageal fistula during conduct of this study to the sponsor, within 24 hours of learning of the adverse event by submitting the adverse event eCRF. The investigator must electronically sign the electronic adverse event form. A copy of medical records, supporting documents (CT scans, ECGs, consult records), death records, death certificates and an autopsy report (if performed) are required to be sent to the AtriCure or designee within 10 days following the death.

Any reported death (determined to be device or procedure related) and atrio-esophageal fistula during the conduct of this study, will be reported to the FDA within 10 days.

In addition, subject deaths (determined to be device or procedure related and atrio-esophageal fistula must be reported to the IRB/EC in accordance with IRB/EC requirements.

In the event of a reported atrio-esophageal fistula study enrollment will be put on pause (see Study Stopping Rules Post-Surgical Ablation).

10.5.4 Study Stopping Rules Post-Surgical Ablation

In the event that a new esophageal injury is adjudicated by the core lab as a thermal injury with perforation related to the study index Epicardial Procedure [e.g., atrio-esophageal fistula or pericardioesophageal fistula or other esophageal perforation but without fistulous connection to the left atrium or pericardial sac] is confirmed between Visit 2 until the start of Visit 7, the following will occur:

- AtriCure will notify the FDA within 10 working days of AtriCure awareness.
- AtriCure will also notify the Site Investigators within 10 working days of AtriCure awareness and immediately pause further Epicardial Procedures and consent of new subjects.

10.6 Safety Monitoring
10.6.1 Safety Monitoring Plan (SMP)

The safety monitoring plan is an internal, protocol specific document that is the primary document outlining study safety surveillance procedures in order to assess the safety of the study device/procedure.. If any serious and unanticipated problems are identified, the FDA will be notified promptly.

10.7 Safety Reporting
10.8 PRODUCT COMPLAINTS

The study has safety reporting oversight by AtriCure medical monitor, Independent adjudicators (CEC committee) and DSMB.

Reporting of product complaints for AtriCure Investigational Devices, AtriCure Non-Investigational Devices and Non-AtriCure Products are described below.

10.9 Product Complaint Definition

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. A product complaint may or may not be associated with an AE/SAE.

10.10 Reporting Product Complaints
10.10.1 Investigational Device Product Complaints

All reported device observations, malfunctions or failures for the AtriCure Bipolar System (except the accessory devices) and AtriClip (PRO1 or PRO2) are required to be documented in the Clindex Database within 10 days of observation of the product complaint and sent via email to pcomplaints@atricure.com. In the event of a suspected observation or device problem, the device shall be returned to the Sponsor for analysis. Instructions for returning the investigational device are included in the Study Reference Manual.

Product complaints related to an investigational product must be reported by the PI to the sponsor on the Complaint Information Form. Epicardial procedure related events within 30 days and Endocardial procedure events within 7 days will also require the same reporting procedure on the

Complaint Information Form.

10.10.2 Non-Investigational Device Product Complaints

All reported device observations, malfunctions or failures for AtriCure Non-Investigational (i.e., Marketed Products) products (Glidepath Tape, Wolf Lumitip dissector and Gillinov Cosgrove Selection Guide) will be reported within 10 days of observation of the Product Complaint via email to (pcomplaints@atricure.com) on the Complaint Information Form. Whenever an event involving an AtriCure device is subject to reporting under that Medical Device Reporting (MDR) regulation, AtriCure shall submit to the FDA the appropriate reports required by MDR within the time frames as identified in 21 CFR Part 803.

10.10.3 Non-AtriCure Product Complaints

In compliance with the requirements of 21 CFR Part 803.30 (MDR), the study site (user facility) should be instructed to report any SAEs associated with the use of other (non-AtriCure) marketed products/devices in this study to the respective manufacturer and, if the SAE involves a death, the complaint should be reported to the manufacturer and to the FDA.

10.10.4 Source Of Product Complaint Data

Means of obtaining product complaint data include review of the subject's medical records or observation by the PI and/or study staff.

11.0 STUDY OVERSIGHT

11.1 Independent Clinical Events Committee (CEC) Adjudication

An independent, non-investigator, clinical events committee comprised of practicing cardiothoracic surgeon, electrophysiologist, and neurologist will act as physician adjudicator(s) under the direction of AtriCure, Inc. This physician(s) will be responsible for the review and validation of reported adverse events that occur over the course of the study per the Independent Clinical Events Committee (CEC) Charter. The clinical events committee adjudicator(s) 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 physician(s) shall be blinded to the clinical site as much as possible. A Clinical Events Committee (CEC) Charter will be developed prior to the start of study enrollment. The CEC Charter shall include consistent definitions for each type of event and shall outline the review process.

SAEs will be submitted for adjudication up to 12 months (Visit 11), after the patient has had their endocardial procedure. In addition, non-serious AEs occurring within 30 days of the epicardial procedure or within 7 days of the endocardial procedure will also be submitted for adjudication. Only SAEs as defined within the Primary Safety Endpoint will be adjudicated until patient exit.

11.2 Data Safety Monitoring Board (DSMB)

The DSMB will be assembled prior to subject enrollment. The DSMB will be compromised of

leading physician practitioners (cardiothoracic surgeon and electrophysiologist) and a biostatistician who are not investigators in the study. The membership of the committee shall remain anonymous to the investigational sites to reduce any potential bias.
In the safety monitoring role, prior to enrollment of any subjects, the DSMB will establish a charter including a mission statement, operating procedures, and proposed monitoring criteria for the study, including any required interim analysis time points for assessing safety and proposed stopping rules. The specific stopping rules shall remain confidential to the site and the Sponsor to minimize bias. Written minutes of all meetings shall be developed after each DSMB meeting and major conclusions shall be documented. Meeting summaries shall be included in reports to the IRBs/ECs as appropriate.

11.3 Core Laboratories

ECG Core Laboratory
An independent ECG core laboratory will be utilized for assessment of the following data collected on subjects. All data submitted to the core laboratory will be reviewed and the core laboratory will interpret the reading.

- Visit 10 and Visit 11: ECG collected at follow-up study visits
- Visit 10 and Visit 11: Continuous ECG monitoring recordings (Holter or ZioTM Patch)
- Visit 10 thru Visit 11: Symptom driven monitoring

All ECG monitoring shall be performed in accordance with the core laboratory's recommended protocol which is provided to the sites in the Study Reference Manual.

Imaging Core Laboratory
Left Atrial Appendage: An independent core laboratory will be utilized for assessment of the complete exclusion of the LAA defined by lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA.
Images to be sent by the site include:

- Visit 5: (TEE) Endocardial Procedure Visit
- Visit 11: (CT/CTA/MRI) 12-month post Endocardial Procedure Visit.

Pulmonary Veins: If a subject exhibits symptoms suggestive of pulmonary vein stenosis, the baseline and subsequent CT/MR imaging will be submitted by the site to an independent imaging core laboratory for analysis.

- Images sent to core lab (as applicable) for Visit 4, Visit 10, Visit 11

Consistent with the recommendation from the 2012 HRS/EHRA/ECAS Expert Consensus Statement in Surgical and Catheter Ablation of AF, PV stenosis is categorized as mild < 50%, moderate 50-70% and severe ≥ 70% reduction in the diameter of a PV or PV branch.

Esophagoscopy Core Laboratory
Esophagoscopy (EGD): An independent core laboratory will be utilized for adjudication of any esophageal injuries discovered on the post epicardial procedure EGD. All data submitted to the core laboratory will be reviewed and the core laboratory will provide adjudication. An esophagoscopy at Visit 2 will be performed as a baseline assessment. An esophagoscopy at Visit 3 is to be performed 24 to 72 hours post Procedure. If the esophagoscopy at Visit 3 reveals a new acute esophageal injury, subject reports, images, data and relevant documents will be submitted to a core lab.

REFERENCE LIST

[1] Calkins H, Brugada J, Cappato R, et al. 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. Heart Rhythm, Vol 9, No 4, April 2012.

[2] Study Group of the Working Group on Valvular Heart Disease of the European Society of Cardiology. Guidelines for prevention of thromboembolic events in Valvular heart disease. Eur Heart J 1995;16;1320-30.

[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]Long-term single procedure efficacy of catheter ablation of atrial fibrillation.Cheema A, Vasamreddy CR, Dalal D, Marine JE, Dong J, Henrikson CA, Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H.*J Intervent Card Electrophy*, 2006;15(3):145-55, Wpuv 2006 Aug 5.

[6]Catheter ablation for atrial fibrillation are results maintained at 5 years of follow-up.Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P. *J Am Coll Cardio*l. 2011 Jan 11;57(2):160-6. doi: 10.1016/j.jacc.2010.05.061.

[7]Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy.Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. *J Am Coll Cardiol*. 2012 Nov 6;60(19):1921-9. doi: 10.1016/j.jacc.2012.04.060. Epub 2012

[8]Cox, J.L., Boineau, J.P., Schuessler, R.B., Kater, K.M., Lappas, D.G.: Five-Year Experience With the Maze Procedure for Atrial Fibrillation. Annals of Thoracic Surgery 56:814-824, 1994.

[9]Cox, J.L., Schuessler, R.B., Lappas, D.G., and Boineau, J.P.: An 8 ½ Year Clinical Experience With Surgery for Atrial Fibrillation. Annals of Surgery, 224(3);267-275, 1996.

[10]Prasad SM, Maniar HS, Camillo CJ, Schuessler RB, Boineau JP, Sundt TM III, Cox JL and Damiano RJ Jr.: The Cox maze III procedure for atrial fibrillation: Long-term efficacy in patients undergoing lone versus concomitant procedures. Journal of Thoracic and Cardiovascular Surgery, 126:1822-27, 2003.

[11] Damiano R, Rochus V. Surgical and minimally invasive ablation for atrial fibrillation. Current Treatment Options in Cardiovascular Medicine. 2006; 8: 371-376.

[12] Mack M. Current results of minimally invasive surgical ablation for isolated atrial fibrillation. Heart Rhythm. 2009; 6: S46-S49.

[13] Gillinov et al. Surgery for permanent atrial fibrillation: Impact of patient factors and lesion set. Ann Thorac Surg. 2006; 82: 502-514.

[14] Han FT, Kasirajan V, Kowalski M, Kiser R, Wolfe L, Kalahasty G, Shepard RK, Wood MA, Ellenbogen KA. Results of a minimally invasive surgical pulmonary vein isolation and ganglionic plexi ablation for atrial fibrillation: single-center experience with 12-month follow-up. Circ Arrhythm Electrophysiol. 2009 Aug; 2(4):370-7.

[15]Zhou J., Scherlag, B.J., Niu, G.,Hou, Y., Z. Zhang, Y., Ding, Y., Lazzara, R., Jackman, W.M. and Po, S.S. (2008) Anatomy and Physiology of the Right Interganglionic Nerve Implications for the Pathophysiology of Inappropriate Sinus Tachycardia. Journal of Cardiovascular Electrophysiology, 19: 971–976. doi: 10.1111/j.1540-8167.2008.01146.x

[16] Haïssaguerre M, Hocini M, Sanders P, et al. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol. 2005 Nov;16(11):1138-47

[17] Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004 Jun 2;43(11):2044-53

[18] Di Biase L, Elayi CS, Fahmy, TS, et al. Atrial fibrillation ablation strategies for paroxysmal patients: Randomized comparison between different techniques. Circ Arrhythm Electrophysiol 2009;2:1134-119.

[19] FDA Drug Safety Communication: Severe liver injury associated with the use of dronedarone (marketed as Multaq) [1-14-011], http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm#additional_information_for_hcps.

[20]U.S. Food and Drug Administration (January 20, 2010) Draft Guidance for Industry and FDA Staff: Heart Valves - Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications. *http*://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM198043.pdf Accessed 01May2014.

[21]Calkins H, Kuck KH, Cappato R, et al. HRS/EHRA/ECAS Expert consensus statement on catheter and surgical ablation of AF: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Heart Rhythm*. 2012;9:632–96.

[22]Hohnloser SH, Pajitnev D, Pogue J, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol*. 2007 Nov 27;50(22):2156–2161

[23]Zembala M, Filipiak K, Kowalski O, et al. Minimally invasive hybrid ablation procedure for the treatment of persistent atrial fibrillation: one year results. *Kardiol Pol*. 2012;70:819-28.

[24]Kiser AC, Landers MD, Boyce K, et al. Simultaneous catheter and epicardial ablations enable a comprehensive atrial fibrillation procedure. *Innovations*. 2011;6(4):243-247.

[25]Gehi AK, Mounsey JP, Pursell I, et al. Hybrid epicardial-endocardial ablation using a pericardioscopic technique for the treatment of atrial fibrillation. *Heart Rhythm*. 2013;10:22-8

[26]Geršak B, Zembala MO, Müller D, et al. European experience of the convergent atrial fibrillation procedure: Multicenter outcomes in consecutive patients. *J Thorac Cardiovasc Surg*. 2014 Apr;147(4):1411-6

[27]Gilligan DM, Joyner CA, Bundy GM. Multidisciplinary Collaboration for the Treatment of Atrial Fibrillation: Convergent Procedure Outcomes from a Single Center. *J Innov CRM*. 2013;4:1396–403

[28]Pison L, La Meir M, van Opstal J, et al. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J Am Coll Cardiol*. 2012;60:54-61

[29]Civello K, Smith CA, Boedefeld W. Combined endocardial and epicardial ablation for symptomatic atrial fibrillation: single center experience in 100+ consecutive patients. *J Innov CRM*. 2013;000:1–7.

[30]FDA Executive Summary (October 27, 2011), Medtronic Ablation Frontiers Cardiac Ablation System P100008,http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM276782.pdf Accessed 01May2014.

[31]Steinhaus DM. Medtronic Cardiac Ablation System P100008. Circulatory System Devices Advisory Panel [PDF of PowerPoint Presentation]. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM277766.pdf Accessed 01May2014.

[32]Eloff BC. BIOSENSE WEBSTER NAVISTAR® THERMOCOOL® Catheter for Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation FDA review of P030031/S11 [PDF of PowerPoint Presentation]. 2008; http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4393s1-01-FDA%20team%20presentation%20FINAL%20(2).pdf Accessed 01May20

[33]Mont L, Bisbal F, Hernández-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J.* 2014;35:501-507.

[34]Tilz RR, Rillig A, Thum AM, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol.* 2012;60:1921-9

[35] G080095 EXCLUDE Clinical Trial (AtriCure Protocol CP2008-2) Device: AtriClip LAA Exclusion Device

[36] Healey, J., Crystal, et.al. Left Atrial Appendage Occlusion Study (LAAOS): Results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke, Am Heart J 2005;150:288-293.

[37] García-Fernández MA, Pérez-David E, et. al. *Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis – a transoesophageal echocadiographic study. J Am Coll Cardiol 2003;42:1253-1258.*

[38] Blackshear JL, Odell JA *Appendage obliteration to reduce stroke in cardiac surgical patients with AF. Ann Thorac Surg 1996;61:755-759.*

[39]Bando K, Kobayashi J, et. al. *Early and late stroke after mitral valve replacement with a mechanical prosthesis: risk factor analysis of a 24-year experience. J Thorac Cardiovasc Surg 2003;126:358-364.*

[40]Schneider B, Stöllberger C, et. al. *Surgical closure of the left atrial appendage – a beneficial procedure. Cardiology 2005;104:127-132.*

[41] Gillinov, M. Pettersson, G., et al. Stapled excision of the left atrial appendage. The Journal of Thoracic and Cardiovascular Surgery. Vol. 129, Number 3, 679-680.

[42] Katz, E. Tsiamtsiouris, T. et. al. Surgical Left Atrial Appendage Ligation Is Frequently Incomplete: A Transesophageal Echocardiographic Study. *J. Am. Coll. Cardiol.* 2000;36;468-471

[43] Oneglia C, Muneretto C, et. al. Transesophageal investigation of surgically ligated left atrial appendage. *Echocardiography*. 2004;21(7):617-619

[44] Topkara VK, Williams MR, et al. Radiofrequency and microwave energy sources in surgical ablation of atrial fibrillation: a comparative analysis. Heart Surg Forum 2006; 9(3):E614-7.

APPENDICES

APPENDIX 1 – CORONARY ANOMALIES

Congenital coronary abnormalities of significance may occur in association with other congenital abnormalities (e.g. supravalvular aortic stenosis, Tetralogy of Fallot, dextro-transposition of the great vessels).

Isolated congenital coronary artery anomalies of ectopic arterial origin, course and distribution are uncommon. Examples include anomalous origin of left coronary artery from the pulmonary artery, coronary artery fistula to any of the four cardiac chambers or great vessels, anomalous origin of a coronary artery from the contralateral sinus of valsalva with traversing of the vessel of the vessel across the base of the heart by passing anterior to, posterior to, or between the aorta and pulmonary artery. Derivation of the entire coronary circulation from a single ostium is a rare coronary anomaly. In this case too, one or more components of the coronary circulation must pass across the base of the heart by passing anterior to, posterior to, or in between the aorta and pulmonary artery.

An intra-atrial myocardial or intra-cavitary anomalous course of the right coronary artery in the right atrium is has been reported. Report of an intra-atrial myocardial or intra-cavitary anomalous course of the left coronary in the left atrium has not been identified.

Observation has been noted in a patient with an anomalous course of the left coronary artery originating from the left sinus of valsalva but coursing posterior away from the pulmonary artery trunk and out onto the roof of the left atrium. The atypically located coronary vessel was contained within left atrial fatty tissue and myocardium and coursed towards the base of the left atrial appendage before traversing up onto the left ventricle and following the usual course with the circumflex artery passing medial to the base of left atrial appendage and the left anterior descending artery onto the left ventricle.

This anomalous course of the left coronary artery on the roof of the left atrium was problematic in that the course of the artery traversed the usual location of the left atrial roof radiofrequency ablation line of the thoracoscopic atrial fibrillation ablation procedure.

To identify patients with atypical and uncommon coronary artery anatomy which may potentially preclude placement of radiofrequency ablation lines along the roof of the left atrium, the following is a standardized pre-intervention evaluation recommended in all patients:

1) All patients in whom catheter-based endocardial ablation or surgical epicardial ablation is being considered undergo a standard CTA with contrast and 6mm cuts for definition of pulmonary vein anatomy.
2) In addition, post-processing imaging with 0.2mm cuts is performed for better definition of coronary anatomy.
3) Radiologic interpretation includes specific mention and description of origin and course of coronary arteries.

Figure 1.
Schematic depiction of normal origin of left coronary artery from left aortic sinus with normal course of left coronary just behind pulmonary artery trunk. Blue bar (—) indicates usual location of a portion of the left atrial roof radiofrequency ablation line, well posterior to and away from the expected usual course of left coronary artery.

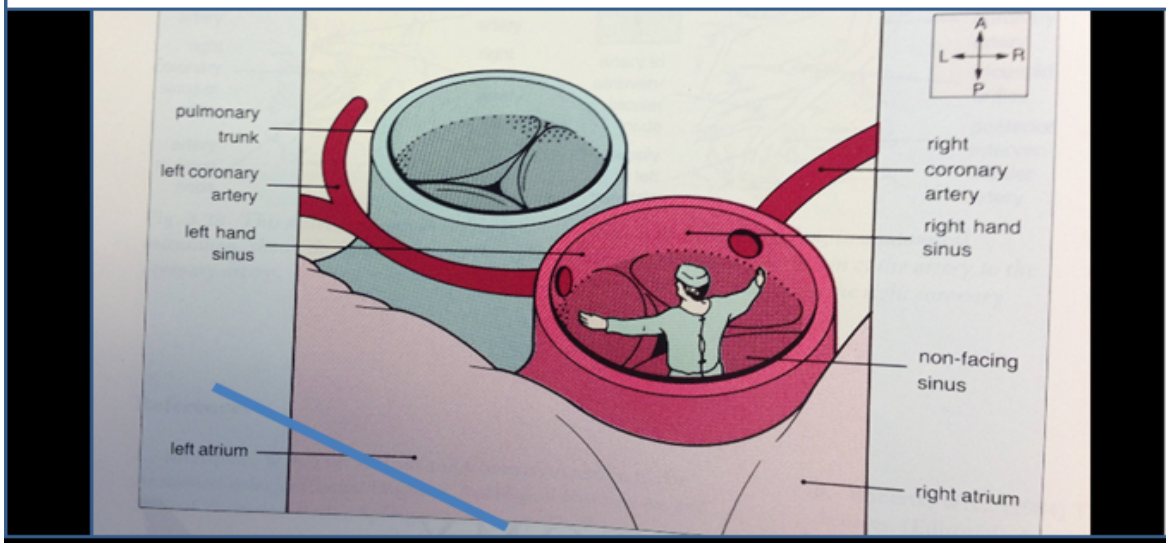


Figure 2b.
Detail of Figure 2a with 6mm cuts, again showing normal course of left coronary artery just posterior to pulmonary artery and well away from roof of left atrium.

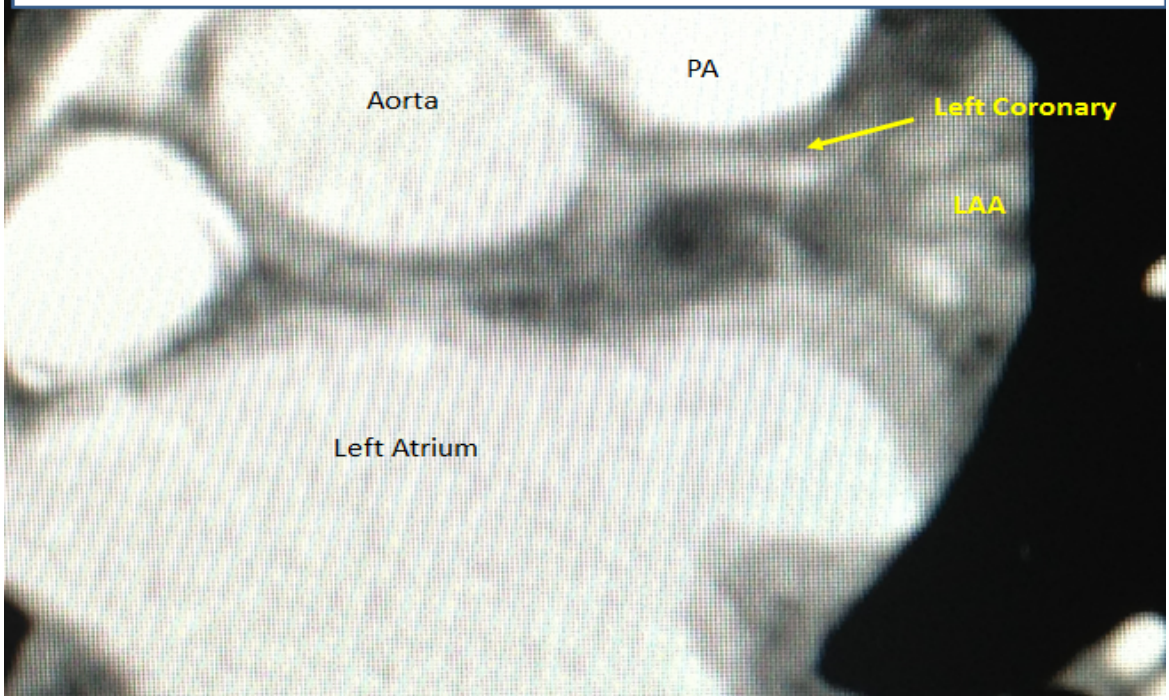


Figure 2a.
CTA (with contrast, 6 mm cuts) demonstrating normal course of left coronary arising from left aortic sinus, passing horizontally and just posterior to pulmonary artery trunk and well away from roof of left atrium.

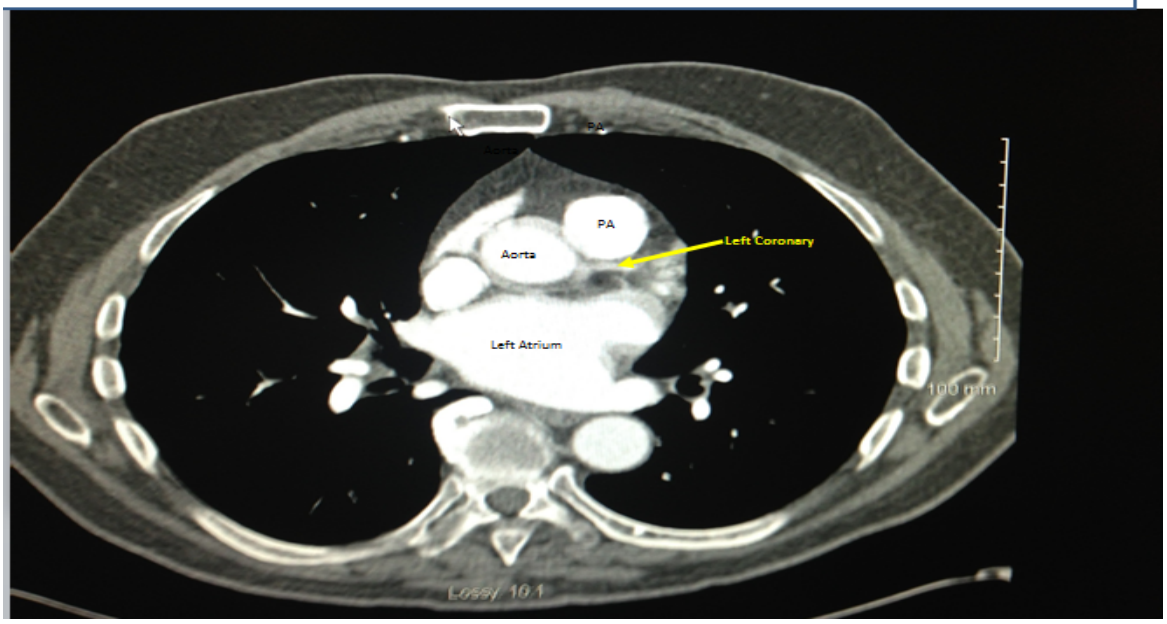


Figure 2c.
Detail of Figure 2a with 0.2 mm cuts for better definition of coronary anatomy, showing normal course of left coronary artery and showing bifurcation into LAD and Circumflex
Coronary Arteries.

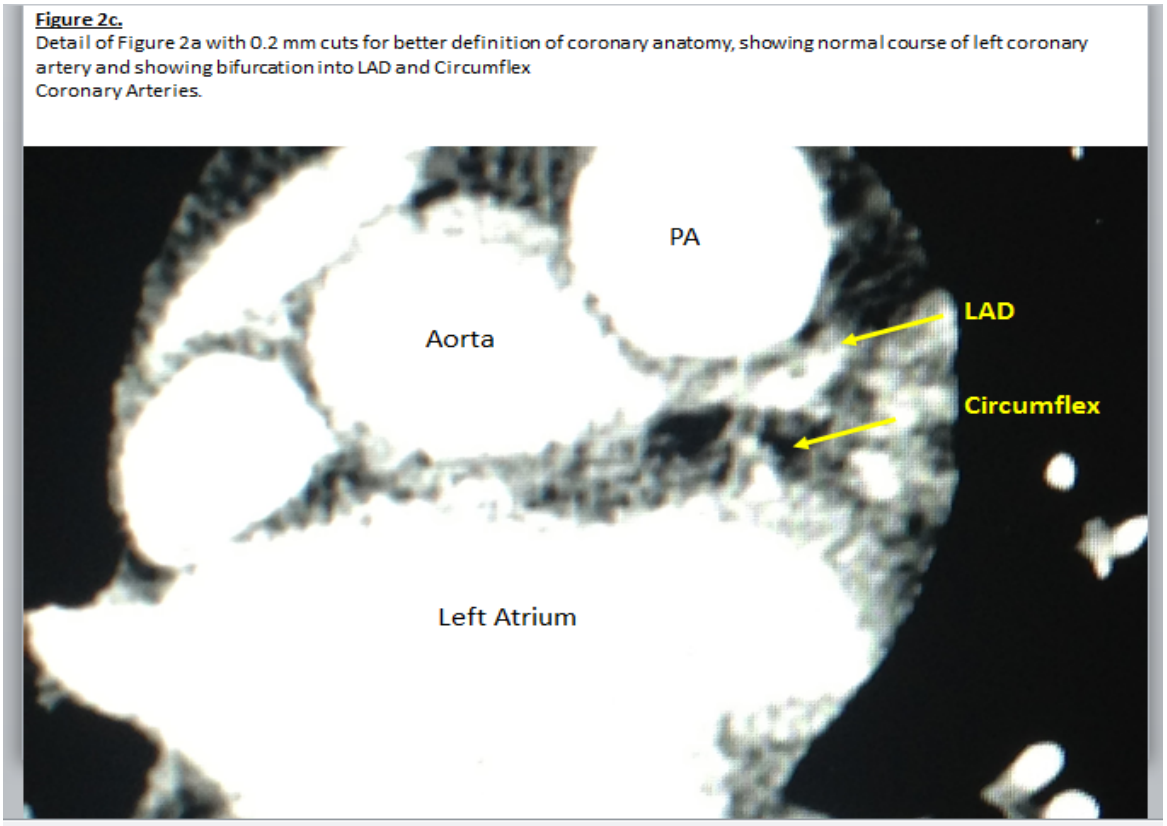
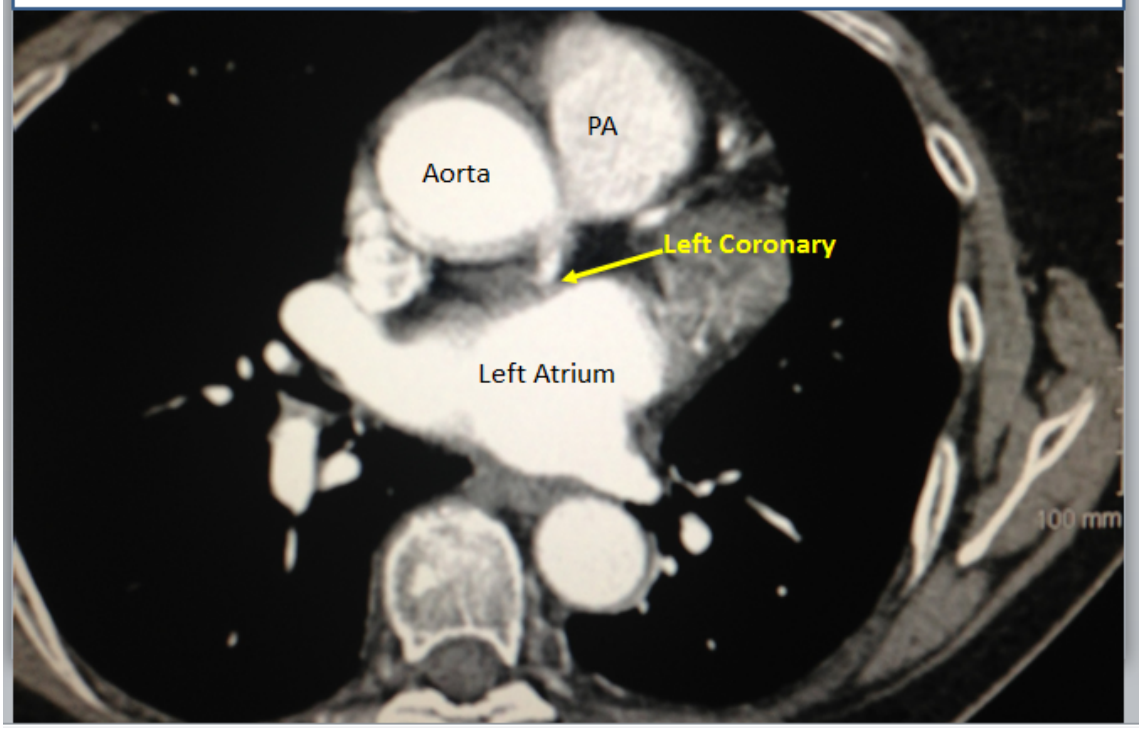


Figure 3a.
CTA in different patient (with contrast, 6 mm cuts) demonstrating anomalous course of left coronary arising from left aortic sinus, but then coursing vertically towards roof of left atrium and away from pulmonary artery trunk.



AtriCure

APPENDIX 2 – AF CLASSIFICATION REVIEW

SAMPLE

AF Classification Review Instructions

To ensure that subjects meet the atrial fibrillation classification criteria per the HRS Expert Consensus Statement[1], the Potential Subject AF Classification Confirmation Form must be completed and faxed to the AtriCure prior to the subject has their epicardial surgical ablation procedure.

The completed form will be reviewed and returned to you noting that the subject is eligible as far as the AF Classification determination (i.e., persistent or longstanding persistent). Likewise, if the subject is deemed ineligible, the reason will be noted. This document will be kept with the subject's source document as evidence of eligibility.

PROCESS FLOW:

The site will:

a) Identify a potential subject for DEEP Pivotal Study (CP2014-1)
b) Review medical records for appropriate supporting source documentation
c) Obtain signed informed consent form by subject prior to submitting source for review
d) Complete the attached AF Classification Confirmation Form
e) **REDACT** patient identifiers (name, medical record number, etc.) from supporting source documentation
f) EMAIL completed form and supporting source documentation at a minimum of 1 week prior to the subject's scheduled epicardial surgical ablation procedure.
Email: deepafclass@atricure.com
g) Await the written response from Review team
h) If eligible, proceed with enrollment process

[1]2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow Up, Definitions, Endpoints and Research Design. Hugh Calkins, MD et al.

Site Contact Information:

Name of Person Completing Form: _____

Phone number where you can be reached: _____

Email address: _____

Informed Consent Signed:

Date: ____/_____/____
DD /MMM/ YYYY

Epicardial Surgical Procedure Date (if known):

Surgery scheduled date: ____/_____/____
DD /MMM/ YYYY

AF Status:

Date of Initial AF Diagnosis: _____/_____/_____
DD / MMM/ YYYY

AF Classification in accordance with HRS AF Expert Consensus Statement (2012)

☐ **Persistent** = is defined as continuous AF that is sustained beyond seven days but no more than one year, or lasting greater than 48 hours and less than seven days but necessitating pharmacologic or electrical cardioversion.

- *Physician's note indicating continuous AF ≥ 7 days but no more than one year, or AF lasting > 48 hours and < 7 days but necessitating pharmacologic or electrical cardioversion; AND*
- *Two electrocardiograms from any form of rhythm monitoring (e.g., 12-lead ECG, Holter, event monitor, Implantable Loop Recorder (ILR), Pacemaker etc.) documenting continuous AF, with electrocardiograms taken at least 7 days apart, for subjects with sustained AF ≥ 7 days.*

☐ **Longstanding Persistent** = is defined as continuous AF of greater than one year duration.

- *Physician's note indicating continuous AF > one year; AND*
- *24-hour Holter or other form of continuous rhythm monitoring (e.g., event monitor, Implantable Loop Recorder (ILR), pacemaker etc.) obtained within 90 days prior to the index procedure showing continuous AF.*

  Note: If subject does not have continuous AF documentation before consent, it can be obtained during the screening period to ensure accurate classification.

  Note: 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 Longstanding Persistent.

_____ _____
#1 Date of Rhythm Assessment **#2 Date of Rhythm Assessment**

Rhythm Assessment(s) Attached:

☐ Holter _____HR ☐ Event Monitor _____Day (s)
☐ ECG ☐ Other: _____

AAD Treatment History

Previously Failed AAD Medication (Specify by checking which Class I or III AAD Medication was failed)

❑ Amiodarone AAD Class: III
❑ Sotalol AAD Class: III
❑ Dronedarone AAD Class: III
❑ Propafenone AAD Class: Ic
❑ Flecainide AAD Class: Ic
❑ Quinidine AAD Class: Ia
❑ Dofetilide AAD Class: III

REVIEWER TO COMPLETE

ELIGIBILITY DETERMINATION	
Date of review	_____/_____/_____ DD MMM YYYY
Subject is eligible to be continued in the study Based upon AF Classification ONLY	☐ YES ☐ NO
AF Classification: ☐ Persistent AF	☐ Long Standing Persistent AF
If no, reason:	
_____ AtriCure Approval Signature	____/_____/_____ DD MMM YYYY

APPENDIX 3 – INVESTIGATOR TRAINING PLAN

Investigator Selection

AtriCure will select investigators who are qualified by training and experience as is required by 21 CFR 812.43(a). In order to be considered for participation in this study the surgeon must be proficient in the MIS/TT cardiac surgical ablation procedure and EPs must be proficient in trans-septal approach for ablation of cardiac arrhythmia.

Investigator Training Program

The DEEP Pivotal Study requires both a Cardiothoracic Surgeon (CTS) and an Electrophysiologist (EP) to complete separate procedures, approximately 91-121 days apart. First an epicardial surgical ablation procedure and then endocardial catheter ablation procedure. Both procedures are required for the treatment to be considered complete, therefore both the surgeon and EP are needed for successful execution of the trial.

All training must be completed prior to treatment of subjects in the study at their site.

The objective of the Investigator Training Program will be to familiarize all DEEP Investigators (Surgeon and EPs) on the DEEP Pivotal Trial Procedure (including the operation and use of investigational devices) and the study protocol. Surgeons will also receive specialized surgical procedure training to ensure they are accomplished on all aspects of the protocol specific surgical procedure. This training program will ensure standardization of surgical techniques for the creation of the DEEP lesion set, an understanding of the principals of EP mapping and ablation and the clinical management of subjects.

A two-phase training program will be conducted. Any Surgeon or EP Instructors utilized in the Moderated Phase (Phase II) of the training program will have recognized and documented expertise in the hybrid (surgical/EP) approach for the treatment of atrial fibrillation and the management of patients who have undergone a hybrid procedure.

Phase I

Surgeon - Self Paced Training Course

Surgeons will complete a self-paced training course. The course will consist of a review of the protocol and the **DEEP Physician Guidebook**, which is a consolidated description of the procedural aspects of the hybrid epicardial surgical procedure showing ablation technique as well as a concentration on dissection and mobilization techniques. The surgeon will also review a video compilation of the surgical technique and the surgical lesion set. Completion of Phase I will be documented (DEEP Pivotal Physician Guidebook Training signature page).

EP – Self Paced Training Course

EPs will complete a self-paced training course using the **DEEP Physician Guidebook.** The course will consist of a review of the protocol, published literature review and a video compilation with animation of surgical technique and protocol defined surgical and EP ablation procedure (i.e., the lesion set). Completion of Phase I will be documented (DEEP Pivotal Physician Guidebook Training signature page).

Phase II

Surgeon - Moderated Training Course

The surgeons will participate in a Moderated Training Course. The didactic training session will

be presented with site initiation and will include:

- Review of the disease state (Persistent & Longstanding Persistent AF)
- Operation/Instructions for Use of Investigational Product
- Details of the procedure (Epicardial Surgical Ablation procedure and Endocardial Ablation procedure)
- Indicators of Procedural success
- Pre- and Post-operative patient care and rhythm status follow-up
- Discussion of best practices for MIS/TT cardiac ablation and the DEEP approach including operative complications (prevention, recognition and management), post-operative subject management and recognition and management of clinical scenarios associated with DEEP.

EP - Moderated Training Course

The EPs will participate in in a Moderated Training Course after the completion of Phase I. The didactic training session will be presented with site initiation and will include:

- Review of the disease state (Persistent & Longstanding Persistent)
- Details of the procedure (Epicardial Surgical Ablation procedure and Endocardial Ablation procedure)
- Indicators of Procedural Success
- Pre- and Post-procedure patient care and rhythm status follow-up
- Discussion of best practices of the DEEP approach including operative complications (prevention, recognition and management), post-procedure subject management and recognition and management of clinical scenarios associated with DEEP.

Completion of Training

Investigators will not be permitted to begin treatment of subjects until they have completed both phases of the training program and have completed the DEEP Pivotal Physician Guidebook Training signature page. Investigators who have substantial experience in the hybrid approach to the treatment of AF and are serving as investigator instructors may begin treating subjects without undergoing investigator training. All investigators, regardless of experience, must participate in the protocol and study specific training provided at the Site Initiation Visit and/or Investigators Meetings as described in the study protocol.

Initial Study Subject Procedures

During all initial Epicardial Surgical Ablation Procedures at a site, a clinical and/or technical expert from AtriCure will be present in the operating room. For investigators who have not had substantial prior experience with MIS/TT surgical cardiac ablation (greater than 15 cases in the preceding 12-month period from site initiation), a proctor will also be present during the initial surgical study procedure. The proctor will be a qualified surgeon who has served as an instructor in the Investigator Training Program or is experienced in the Epicardial Surgical Ablation Procedure and in the use of the AtriCure product line.

APPENDIX 4 – CLINICAL RISK / BENEFIT ANALYSIS

1.0 SUMMARY

The objective of this study is to establish the safety and effectiveness of a dual epicardial and endocardial ablation procedure for patients presenting with Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation utilizing the AtriCure Bipolar System and AtriCure Left Atrial Appendage (LAA) Clip in an endoscopic procedure, followed by an endocardial mapping and ablation procedure utilizing commercially available RF based ablation catheters. The endocardial procedure will be staged to occur after 90 days post epicardial surgical procedure.

Ablation procedures are commonly performed and are a well-accepted treatment for subjects with AF, with a well-established risk profile. Risks to subjects undergoing endoscopic and/or other minimally invasive ablation surgery and EP procedures are listed below. The risks of participation are offset by the significant potential for clinical and functional benefits to subjects with AF that comes through restoring sinus rhythm.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects.

2.0 POTENTIAL BENEFITS

The potential benefit to study subjects outweighs the risks of participation in this study. The benefits may include but are not limited to, the following:

- **Clinical improvement:** restoration of sinus rhythm, improvement of ejection fraction, stroke risk reduction, and survival benefit.
- **Functional improvement:** improvement in quality of life and exercise tolerance
- Overall advancement of medical and scientific knowledge that may benefit future patients with similar conditions may be gained through this clinical study.

There may also be other benefits that are unforeseen at this time.

3.0 POTENTIAL RISKS

Adverse events that may be anticipated in this clinical study are believed to be consistent with those associated with other minimally invasive surgical and catheter-based EP procedures.

Complications may occur at any time during the procedures, post procedures or follow-up period.

Possible adverse events may include, but are not limited to, the following:

- Ablation or burns to non-targeted tissues
- Acute ischemic myocardial event
- Air embolism
- Allergic reaction to implant materials
- Anesthesia risks
- Aneurysm

- Arterial or venous dissection and/or perforation
- Arterial rupture
- Arterial spasm
- Atrio-esophageal fistula
- Arteriovenous fistula
- Atelectasis
- Atrial rupture
- Bleeding requiring intervention to repair
- Cardiac perforation
- Cardiac tamponade (if either open or catheter drainage is required)
- Cardiac Valve or Coronary Artery Injury
- Cerebrovascular accident (STROKE) or other neurologic event
- Chest pain/discomfort
- Conduction disturbances (SA/AV node)
- Congestive heart failure
- Damage to adjacent nerve and/or blood vessels
- Death
- Deep sternal wound
- Drug or Contrast Media Reaction
- Diaphragmatic paralysis (unilateral or bilateral)
- Drug Reaction (significant reaction to any study related medications requiring treatment, including allergic reaction and anaphylactic shock)
- Emergency during the operation requiring change in the planned surgical access
- Endocarditis (bacterial)
- Excessive pain and discomfort
- Excessive bleeding related to the procedure (defined as bleeding which requires > 2 units of blood products and/or surgical intervention)
- Extension of cardiopulmonary bypass
- Extension of extracorporeal bypass
- Esophageal rupture
- Excessive bleeding
- Extravasation of contrast media
- Formation of unwanted scar tissue
- Gastro-intestinal bleed
- Gastric motility disorders
- Hematoma
- Hemothorax
- Hemorrhagic stroke secondary to anticoagulant therapy
- Hypertension
- Hypotension
- Infection or fever

- Injury to the heart, a blood vessel, or other part of the body due to the investigational device, possibly requiring intervention.
- Intercostal nerve injury
- Ischemia
- Major infection (i.e., of the chest wall, mediastinum, etc.)
- Mitral valve injury
- Myocardial infarction (MI)
- New Arrhythmia other than AF needing medical treatment or intervention as treatment (including bradycardia and left atrial flutter and excluding right atrial flutter)
- New onset or exacerbation of existing Congestive Heart Failure
- New Sinus Node Dysfunction
- Newly developed second- or third-degree AV block requiring permanent pacemaker
- Pericarditis requiring re-operation
- Persistent Chest Pain (post discharge surgical incision pain, not angina)
- Pericardial Effusion
- Phrenic nerve injury
- Pneumonia (confirmed by imaging)
- Pneumothorax (requiring intervention)
- Post-surgical Atelectasis (major lung tissue collapse with significant symptoms such as cyanosis, extreme shortness of breath, dyspnea, and/or stabbing pain on the affected side)
- Postoperative embolic complications
- Pseudoaneurysm
- Pulmonary vein stenosis (confirmed by imaging indicating 70% narrowing in diameter of any one pulmonary vein or 50% narrowing of diameter in two or more pulmonary veins.)
- Pulmonary Edema
- Pulmonary embolism
- Pyloric spasm disorder
- Radiation exposure or injury
- Reaction to contrast media/ medication
- Recurrent laryngeal nerve injury
- Renal insufficiency or failure
- Respiratory distress or failure (breathing problems)
- Sepsis
- Serious injury or surgical intervention
- Serious skin burn
- Significant Chest Wound Infection (requiring intervention and/or antibiotics)
- Sternotomy
- Stroke (resulting in neurological deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing infarction)
- Thoracotomy

- Thromboembolism (including a deep vein thrombosis or pulmonary embolus)
- Transient Ischemic Attack (TIA) or a neurological deficit lasting less than 24 hours, and if an imaging study is performed showing no evidence of infarction
- Tracheal esophageal trauma
- Unanticipated Device effect
- Vascular access site complications (e.g., hematoma, pseudoaneurysm)
- Ventricular Arrhythmia (V. tachycardia or V. Fibrillation)
- Ventricular perforation or rupture
- Vagal nerve injury
- Wound Infection at surgical site requiring re-operation for wound debridement

There may also be other risks that are unforeseen at this time.

4.0 MINIMIZATION OF RISKS

Measures which will be taken to minimize risks related to the study include:

- The investigators in this study will be selected based on their experience in treating patients with AF and performing surgical treatment procedures, including cardiac ablation procedures.
- Cardiothoracic surgeons will be trained and adept in proper procedure performance and device operation.
- Electrophysiologist selected for participation will be proficient in the performance of transseptal catheter ablation procedures
- Anesthesiologist will be proficient in the placement of double lumen tube intubation
- Well-defined clinical study protocol, including specific inclusion/ exclusion criteria to enroll appropriate subjects in the trial.
- Close patient monitoring following the surgical procedure and EP procedures.
- Ongoing monitoring of study data and results, including the use of an Independent Physician Adjudicator and Data and Safety Monitoring Board.
- Patients will receive education on risks associated with the study.

5.0 CONCLUSION

Based on previous feasibility data and published literatures this treatment showed significant benefits based on overall clinical and functional improvement. This clinical study is justified because the study sponsor and clinical investigators believe the potential benefits outweigh the potential risks.

APPENDIX 5 – ADVERSE EVENT DEFINITIONS

BLOOD AND LYMPHATIC SYSTEM DISORDERS

Anemia: Hematocrit below 25%.

Coagulopathy: Bleeding in the presence with abnormal clotting studies.

Hemodilutional Anemia: Anemia associated with fluid volume overload as a result of cardiopulmonary bypass.

HIT (Heparin Induced Thrombocytopenia): Low blood platelet count as a result of the medication heparin. Must have lab evidence of HIT +.

Leukopenia: Leukopenia is defined as leukocyte count of < 3.5 x10^9/liter for more than 3 days.

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

Thrombocytopenia: A persistent decrease in the number of blood platelets. This is not considered to be an AE until treated.

CARDIAC DISORDERS

Arrhythmias (other than Atrial Fibrillation / Atrial Flutter or Atrial Tachycardia)

Bradycardia: Abnormally low heart rate (<60 bpm) requiring treatment (implantation of a temporary or permanent pacemaker, or medication).

SVT: Tachycardia in which QRS is narrow and P waves are present and associated. In certain SVT's the QRS may be wide (>120msec) when it is aberrant and in some the P wave may be invisible as it maybe superimposed on the QRS (AV Nodal Reentrant Tachycardia).

Ventricular tachycardia (VT): A regular heart rhythm originating from the ventricle with a frequency of 160 to 200 beats per minute that requires intervention.

Ventricular fibrillation (VF): A rapid irregular ventricular rhythm due to multiple reentrant activities associated with essentially zero cardiac output.

Atrioventricular (AV) Block 2nd degree: Second-degree (AV) block is characterized by interruption of impulse conduction through the AV node. This may take the form of progressive prolongation of the P-R interval until there is a nonconducted beat with no QRS (Mobitz I or Wenckebach) or intermittent non-conducted P waves without preceding prolongation of the P-R interval or subsequent shortening of the interval (Mobitz II). This excludes block due to premature atrial beats.

3rd degree: Third-degree AV block (complete heart block) exists when more P waves than the QRS complexes exist, and no relationship exists between them (no conduction).

Angina: A tight or heavy feeling in the chest, discomfort which spreads from the chest to the arm,

back, neck, jaw, or stomach, numbness or tingling in the shoulders, arms or wrists, shortness of breath, and nausea.

Atrial thrombus: Thrombus formation or detection within the atrium.

Cardiac Arrest: Absent or inadequate contraction of the left ventricle of the heart that immediately causes body wide circulatory failure.

Cardiac Tamponade (Pericardial effusion): Defined as the development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise and requires elective or urgent pericardiocentesis. A pericardial effusion of 1 cm or more (by echocardiography) will also be considered a significant pericardial effusion. Pericardial effusion should also be classified as "early" or "late" depending on whether it is diagnosed during or following initial discharge from the hospital. Documentation of CT Scan/MRI/ECHO findings and subsequent treatment such as thoracentesis or pericardiocentesis.

Cardiogenic Shock: Patient exhibits cardiogenic shock (systolic pressure < 80mm Hg and PCWP > 20mm Hg or cardiac index <1.8 liters/minute/m^2 or intra-aortic balloon pump or intravenous inotropes are needed to maintain a systolic pressure>80 mm Hg) for any time within 24 hours prior to index procedure.

Congestive Heart Failure: Documentation of one of the following:

- Paroxysmal nocturnal dyspnea (PND)
- Dyspnea on exertion (DOE) due to heart failure
- Elevated PCW with associated SOB or x-ray consistent with congestion.

May be related to fluid overload in the presence of underlying cardiovascular disease.

Heart Failure: A clinical syndrome resulting from a cardiac disease which comprises ventricular systolic or diastolic function or both. Heart failure results when the heart is unable to generate a cardiac output sufficient to meet the demands of the body without unduly increasing diastolic pressure. Heart failure may be manifested by symptoms of poor tissue perfusion alone (i.e., fatigue, poor exercise tolerance, confusion) or by both symptoms of poor tissue perfusion and congestion of vascular beds (e.g., dyspnea, chest rales, pleural effusion, pulmonary edema, distended neck veins, congested liver, peripheral edema). We will not distinguish between congestive and chronic heart failure for purposes of this protocol.

Myocardial Infarction:
The diagnosis requires at least one of the following:
1. Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following:
    a) Ischemic symptoms
    b) Development of pathological Q waves in the ECG
    c) ECG changes indicative of ischemia (ST segment elevation or depression)
    d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and/or
2. Pathological findings of an acute myocardial infarction.

Myocardial Infarction in the context of catheter or surgical AF Ablation: The presence of any one of the following criteria:

1. Detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB), which may persist for more than one hour;
2. Development of new pathological Q waves on an ECG;
3. Imaging evidence of new loss of viable myocardium or new regional wall abnormality

Pericardial effusion/bleeding: Fluid detected in the pericardial space by standard imaging techniques (e.g., echocardiography) with hemodynamic compromise and requiring treatment with pericardiocentesis.

Pericarditis: Irritation or inflammation of the pericardium associated with pain on inspiration and shortness of breath. Clinical signs may include shallow respiration, pericardial friction rub and ECG changes (ST elevation across the precordial leads).

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.

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 instable angina, occurs at rest or with less exertion than instable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

GASTROINTESTINAL/GENITOURINARY DEFINITIONS

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 an air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan are the most common methods of documentation of an atrial esophageal fistula. An esophagoscopy should NOT be performed as it may result in air insufflation into the left Atrium.

Aortoesophageal Fistula: Abnormal passage from aorta communicating with the esophagus (for the purposes of the protocol - likely resulting from an esophageal perforation or burn). Presentation of aortoesophageal fistula may include hematemesis (possibly massive). Diagnosis may be obtained with a contrast CT scan, aortography, esophagoscopy, or barium swallow. A possible outcome of aortoesophageal fistula is sepsis, which may be diagnosed with blood cultures.

Esophageal Dyskinesia: diffuse spasms of the esophagus which may occur as the result of vagal nerve injury

Esophageal Injury: Any evidence of a mild complication such as erosion or ulceration or a major complication such as puncture, dissection, or perforation to the esophagus.

Gastric Motility Disorders: multiple gastric disorders may occur post AF ablation such as constipation, atony, weight loss, early satiety, diarrhea or GI disturbance.

Gastroparesis: delayed gastric emptying resulting in paresis of the stomach. As the vagus nerve controls the contractions of the stomach, this may occur when the vagus nerve is damaged, and the muscles of the stomach and intestines do not work normally.

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.

Renal Complications:

Renal Failure: Inability of the kidneys to filter toxins resulting in a serum creatinine increase to > 2.0 mg/dl and one of the following:

- increase of 2.0 mg/dl in serum creatinine over any previous value
- 50% or greater increase in creatinine over baseline procedural value
- requirement for dialysis

Renal Insufficiency: An increase in serum creatinine of ≥1.0 mg/dl over previous value.

Renal failure that requires dialysis: a significant decrease in renal function requiring dialysis.

Retroperitoneal Hemorrhage: Bleeding into the retroperitoneum characterized by signs such as hypotension, decreasing hemoglobin, abdominal distention, peritoneal signs, flank and/or hip pain, and increasing bruising.

Vomiting: The ejection of matter from the stomach in retrograde fashion through the esophagus and mouth.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

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.

Drug Reactions: 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.

Fatigue/Malaise: Weariness, tiredness, or lack of energy. Generalized feeling of discomfort, illness, or lack of well-being.

Fever: A temperature > 101°F 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.

Medication Reaction: An unwanted or harmful side effect experienced following the

administration of 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.

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

Non-ischemic Chest Pain: Any discomfort in the chest, shoulder, back or chest wall for which a cardiac ischemic origin is ruled out or not suspected. May be cardiac (for example pericardial) or non-cardiac (for example gastrointestinal) in origin.

Pain at Catheter Insertion Site: Pain at access site determined to be associated with the device or procedure.

Pain: Reports of pain, ranging from mild discomfort to acute agony, may be generalized or localized, requiring treatment or intervention.

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

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.

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

Death: All-cause mortality. Death is not an adverse event; it is an outcome. The Adverse Event is what caused the death.

HEPATOBILIARY DISORDERS

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 Warfarin (Coumadin) treatment) and hypoalbuminemia (Albumin < 3).

IMMUNE SYSTEM DISORDERS

Allergic Reaction: A reaction to a foreign protein characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, or general collapse (anaphylaxis).

INFECTIOUS/INFLAMMATORY DEFINITIONS

Bacteremia: Presence of viable bacteria in the circulating blood without systemic manifestation (sepsis).

Endocarditis: An infection for which no source is identified associated with classic signs of endocarditis (positive blood cultures, fever, red blood cell casts in urine, splinter hemorrhages in

fingernails, roof of mouth, lesions on retina, etc.) associated with a vegetation inside the atrium or on a valve which may be confirmed in echocardiography.

Infection: The following are the categories for infections:

- **Deep Sternal**: involving muscle, bone, and/or mediastinum
- **Deep Sternal Wound Infection**: Infection involving the sternum and/or mediastinum as documented by clinical examination and culture which may require reoperation with sternal debridement and/or sternal rewiring.
- **Thoracotomy Site:** involving a thoracotomy
- **Lung:** involving airways associated with intubation or other respiratory causes
- **Leg:** involving a leg vein harvest site.
- **Major:** Including the chest wall, heart valves, mediastinum, etc., culture proven infection or presumptive treatment with antibiotics for clinically diagnosed infection
- **Minor:** Temperature > 101°F /38.5°C or higher and a positive culture (e.g., tissue, urine, etc.)
- **Catheter Puncture Site:** Infection at the catheter site used for the procedure
- **Endoscopic Puncture Site**: Infection at the puncture site for the ablation procedure
- **Or Systemic Infection:** Bloodstream infection caused by bacteria.

Mediastinitis: The diagnosis requires at least one of the following: (1) an organism isolated from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis seen during an operation; (3) one of the following conditions: chest pain, sternal instability, or fever (>38 ◦ C), *in combination with* either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of mediastinal drainage.

Pneumonia: Pneumonia diagnosed by one of the following: Positive cultures of sputum, blood, pleural fluid, emphysema fluid, transtracheal fluid or transthoracic fluid; consistent with the diagnosis and clinical findings of pneumonia. Should include chest x-ray diagnostic of pulmonary infiltrates.

Sepsis: Culture-proven blood infection manifested by severe systemic symptoms (e.g., fever, hyperventilation, tachycardia, confusion).

Septic Shock: Sepsis with hypotension despite adequate fluid resuscitation. In addition, two or more of the following must be present:

- tachycardia
- temperature < 36° or > 38°C
- hyperventilation
- WBC < 4000 or > 12000

Urinary Tract Infection: Positive urine cultures requiring antibiotic therapy.

Viral Illness: Diseases caused by a virus, including Bronchitis, Sinusitis, Cellulitis, and Upper Respiratory Infection.

INJURY, POISONING AND PROCEDURAL COMPLICATIONS

Atrial Tear: Any evidence of a tear or damage to the two upper chambers of heart/atrium

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

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

Dissections: Presence of angiographically evident intimal disruption (e.g., linear luminal density or luminal staining or linear intraluminal filling defect) which requires treatment.

Ventricular Perforation or Rupture: Any evidence of puncture/dissection/perforation or damage to the ventricle.

Pseudoaneurysm: Compartmentalized blood contiguous with arterial lumen documented by ultrasound or visualized at repair.

Skin Burns:

Second degree burns manifest as erythema with superficial blistering of the skin. Level of pain is dependent upon the level of nerve involvement.

Third-degree burns: occur when the epidermis is lost with damage to the subcutaneous tissue. This burn may exhibit charring and extreme damage of the epidermis, and sometimes hard eschar will be present.

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

METABOLISM DISORDERS

Hyperglycemia: The use of insulin in the post op period does not constitute hyperglycemia if during the same hospitalization. An Elevated blood sugar ≥ 250 in the post-operative constitutes hyperglycemia.

Hypoglycemia: Low blood glucose or low blood sugar, occurs when blood glucose drops below normal levels (50mg/dL).

NERVOUS SYSTEM DISORDERS

Headache: a term used to describe aching or pain that occurs in one or more areas of the head, face, mouth, or neck. Headache can be chronic, recurrent, or occasional.

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

Recurrent Laryngeal Nerve Injury: Symptomatic hoarseness with documented laryngoscopy showing paralyzed or impaired laryngeal cord movement, beyond 30 days post procedure.

Phrenic Nerve 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 at 12 months or longer following ablation.

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

Stroke: Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, 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 neurological deficit lasting ≥ 24 hours, or lasting <24 hours if therapeutic intervention(s) were performed (i.e., thrombolytic therapy or intracranial angioplasty; or available neuro imaging documents a new hemorrhage or infarct or the neurological deficit results in death. Confirmation of the diagnosis by at least one of the following; neurology or neurosurgical specialist, neuro imaging study showing tissue injury or lumbar puncture demonstrating intracranial hemorrhage.

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

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

Vagal Nerve Injury: see esophageal dyskinesia and gastroparesis

Vasovagal Reaction: Reflex stimulation of the vagus nerve causing slowing of the heartbeat, decreased blood pressure, 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.

PSYCHIATRIC DISORDERS

Anxiety: A psychiatric disorder causing feelings of mental discomfort, for example, panic disorder, post-traumatic stress disorder or depression.

RESPIRATORY/PULMONARY

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.

Atelectasis: (post-surgical) is a collapse of lung tissue affecting part or all of one lung; the alveoli are deflated. This is an AE when treatment other than Chest PT is required or it prolongs hospitalization.

Diaphragmatic paralysis: may be unilateral or bilateral. Usually caused by injury to the phrenic nerve as a result of trauma to the thoracic cage. Findings include decreased air flow, dullness to percussion, and absence of diaphragmatic excursion on the ipsilateral side. Diagnosis may be

made with fluoroscopy in which a quick “sniff” (i.e., patient inspiration) results in observation of paradoxical elevation of the ipsilateral diaphragm. Often causes shortness of breath on activity.

Hemoptysis: A cough that produces bloody sputum.

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 required.

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: Pulmonary embolism diagnosed by study such as V/Q scan or angiogram or spiral CT or clinical symptoms consistent with PE in the absence of these studies that result in treatment.

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 as 70% diameter stenosis of one pulmonary vein or 50% diameter 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).

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.

Respiratory insufficiency: Deterioration of patient’s respiratory efforts that require supportive or medical treatment.

VASCULAR DEFINITIONS

Atrial Embolism: Angiographic evidence of embolic occlusion in any arterial distribution.

Arterial Occlusion/Thrombosis at Access Site: Angiographic or ultrasonographic evidence of occlusion at the access site,

Arteriovenous Fistula: A traumatic communication between an artery and vein documented by ultrasound or angiography

Post-Operative Excessive Bleeding: Defined as 2 or more units of blood transfused in a 24-hour period, or reoperation to control bleeding, in the first 7 days post-index surgical procedure.

Deep Vein Thrombosis (DVT): Angiographic or ultrasonographic evidence of thromboembolic occlusion in the lower extremities.

Embolism (including air emboli and thromboemboli): The blockage of an artery by an embolus, which can include a thrombus or an air bubble.

Hematoma: Development of a collection of blood > 5 cm's under the skin requiring compression or additional treatment to resolve.

Hemorrhage: Any bleeding which results in a drop in hematocrit from pre-procedure level of greater than or equal to 6 points (2 grams of HGB) or a Hct < 30, or blood loss that requires transfusion or results in substantial hemodynamic compromise requiring treatment. Hemorrhage will be considered serious if it requires > 2 units of blood in a 24-hour period or results in hemodynamic compromise.

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

Hypotension: Any prolonged systolic blood pressure < 80 mmHg associated with symptoms and requiring intravenous vasopressor medications.

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.

Peripheral Ischemia: Deficient supply of blood to the blood vessels outside the heart and brain that is due to obstruction of the inflow of arterial blood.

Post-Operative Late Bleeding: Hemorrhage requiring > 2 units beginning 48 hours after procedure through 30 days and attributed to index procedure.

Procedural Bleeding: Bleeding occurring during the procedure requiring 3 or more units of blood transfused, beginning within the operating room and ending 48 hours after the procedure (attributed to index procedure).

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.

Thrombophlebitis: Inflammation of a vein with formation of a thrombus.

Thrombus: Blood clot that obstructs a blood vessel.

APPENDIX 6 – DEEP Pivotal Subject Flow Chart (Rev. E)