AtriCure

AtriCure, Inc.
7555 Innovation Way
Mason, Ohio 45040

Outcomes of Surgical AF ablation using CryoICE cryoablation system
FREEZE-AFIB POST-MARKET STUDY
CLINICAL TRIAL PROTOCOL: CP-2021-02

Revision Number	A
Date	August 2, 2021
National Principal Investigator/Lead Principal Investigator:	Dr Evelio Rodriguez, M.D. Saint Thomas Heart Hospital 4230 Harding Road, Suite 530 Nashville, TN 37205 United States 1 615 222-5592
Study Oversight Committee	National PI(s) & AtriCure Medical Advisor
Planned Number of Sites and Region(s) (US/OUS)	Up to 150 subjects will be enrolled at up to 20 sites in the US, United Kingdom (UK) and/or Europe (EU)
Clinical Investigation Type	Retrospective-prospective, multi-center, non-randomized, unblinded, post-market study to evaluate the safety and long-term performance of CRYOF during concomitant AF ablation
AtriCure Medical Advisor	**Sydney Gaynor** Medical Director of Clinical Education, Clinical AtriCure, Inc. 7555 Innovation Way, Mason, OH 45040 M. 513-560-5974 SGaynor@atricure.com
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Electronic Data Capture Software	Clindex®
Core Laboratories	Medicomp, Inc
Independent Physician Adjudicator(s)	To be Determined
Protocol Author	Erik Fransen, Director, Clinical Science International

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SPONSOR SIGNATURE PAGE

Trial Name	FREEZE-AFIB Study
Trial Number:	CP-2021-02
Title:	Outcomes of Surgical AF ablation using CryoICE cryoablation system
Test Articles:	AtriCure® CryoICE cryoablation system comprised of: • cryoICE® cryoFORM cryoablation probe, CRYOF • AtriCure® Cryo Module (ACM1/ACM2)

Approvals:

Aug 6, 2021

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VP Clinical Affairs & Biometrics
AtriCure, Inc.

Aug 6, 2021

Sydney Gaynor, MD Date
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Aug 6, 2021

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

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met
- Conduct the trial in accordance with this protocol, including applicable local/state laws and regulations
- Provide a copy of the Financial Disclosure form that summarizes financial interest in the AtriCure cryoICE cryoablation system
- Complete all Case Report Forms and study documentation, and relevant assessments (as required) promptly to the Sponsor, AtriCure, Inc., or its authorized representatives
- Adhere to the publication policy of AtriCure, as stated in the Clinical Study Agreement, for data collected during this trial
- Ensure that all associates, colleagues, and employees of AtriCure assisting in the conduct of the trial(s) are informed of their obligations in meeting the above commitments
- 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 have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal/Co-Investigator

Printed name:
Signature:
Date:

Please return the signed original to:

Dr. Erik Fransen
Director, Clinical Science International
AtriCure, Inc. (Sponsor)
7555 Innovation Way
Mason, Ohio 45040

AtriCure

NATIONAL PRINCIPAL INVESTIGATOR/LEAD PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met
- Conduct the trial in accordance with this protocol, including applicable local/state laws and regulations
- Provide a copy of the Financial Disclosure form that summarizes financial interest in the AtriCure cryoICE cryoablation system
- Complete all Case Report Forms and study documentation, and relevant assessments (as required) promptly to the Sponsor, AtriCure, Inc., or its authorized representatives
- Adhere to the publication policy of AtriCure, as stated in the Clinical Study Agreement, for data collected during this trial
- Ensure that all associates, colleagues, and employees of AtriCure assisting in the conduct of the trial(s) are informed of their obligations in meeting the above commitments
- Propose to the sponsor any appropriate modification(s) of the protocol or investigational device, or of the use of the investigational device

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

National Principal Investigator / Lead Principal Investigator

Printed name:
Signature:
Date:

Please return the signed original to:

Dr. Erik Fransen
Director, Clinical Science International
AtriCure, Inc. (Sponsor)
7555 Innovation Way
Mason, Ohio 45040

FREEZE-AFIB PROTOCOL SYNOPSIS

Regulatory Classification	Post-Market Study
Indication	The AtriCure cryoICE® cryoFORM™ cryoablation probe is indicated for use in the cryosurgical treatment of cardiac arrhythmias by freezing target tissues, creating an inflammatory response (cryonecrosis) that blocks the electrical conduction pathway.
Clinical Investigation Name and Number	FREEZE-AFIB Post-Market Study CP-2021-02
Title	Outcomes of Surgical AF ablation using cryoICE cryoablation system
Objective(s)	The primary objective of this study is to evaluate the safety and performance of cryoFORM (CRYOF) device. The performance of the device will be demonstrated by establishing that the device effectively eliminates persistent and long-standing persistent atrial fibrillation in a clinically significant proportion of treated patients.
Device(s) Under Investigation	AtriCure® CryoICE cryoablation system is comprised of: • cryoICE® cryoFORM™ cryoablation probe, CRYOF • AtriCure® Cryo Module (ACM1/ACM2)
Rationale	This study is proposed herein is to gather clinical data on the safety and performance of the CRYOF device. Specifically, data from this study will be used for submission to regulatory authorities in Europe, China and other geographies as needed.
Number of Subjects/Sites Required for Inclusion in Clinical Investigation	Up to 150 subjects will be enrolled at up to 20 sites in the US, UK and/or EU.
Clinical Investigation Design	Retrospective-prospective, multi-center, non-randomized, unblinded, post-market study to evaluate the safety and long-term performance of CRYOF during concomitant AF ablation.
Subject Population	Patients who have undergone concomitant surgical AF ablation using the CRYOF device under investigation.
Justification of Sample Size and Performance Goal	Based on a performance goal (PG) of 55%, expected success rate of 68% and attrition rate of 6.5% at the last follow-up visit post procedure, a sample size of 150 patients provides at least 88% power to demonstrate primary performance success. In addition, based on a performance goal of 15% for safety, expected

	MAE rate of up to 8.5%, the sample size provides 80% power to demonstrate primary safety success. Published literature on the safety and effectiveness of the concomitant AF ablation during cardiac surgical procedure was used to derive the performance criteria for the trial.
Inclusion Criteria	1. Subject is greater than or equal to 18 years of age. 2. Subject has documented history of atrial fibrillation. 3. Subjects who received surgical ablation for their atrial fibrillation using CRYOF and on whom at least the following lesions were performed: left and right pulmonary vein isolation, roof and floor lines, mitral annulus line, a connecting lesion from left atrial appendage to left pulmonary vein, coronary sinus lesion and LAA exclusion, with a lesion duration of at least 2 minutes. 4. Stable subject that underwent non-emergent cardiac surgical procedure(s) on cardiopulmonary bypass including open-heart surgery for one or more of the following: mitral valve repair or replacement, aortic valve repair or replacement, tricuspid valve repair or replacement, or coronary artery bypass procedures, or atrial septal defect (ASD) repair. 5. Left Ventricular Ejection Fraction ≥ 30% (determined by echocardiography or cardiac catheterization performed within 90 days of enrollment as documented in patient medical history). 6. Subject is willing and able to provide written informed consent. 7. Subject is willing and able to return for scheduled follow-up visits.
Exclusion Criteria	1. Stand-alone AF without indication(s) for concomitant CABG and/or valve surgery. 2. Previous left sided ablation procedures prior to surgical ablation. 3. Untreated atrial flutter and symptomatic ventricular arrythmia. 4. Known carotid artery stenosis greater than 80% prior to index ablation procedure. 5. Prior history of ischemic stroke or hemorrhagic stroke. 6. History of MI with ST elevation within 6 weeks prior to the index ablation 7. Documented AF duration of greater than 10 years. 8. Large left atrial size i.e., LA diameter >7 cm prior to the index ablation procedure. 9. Subjects with active systemic infection prior to index ablation procedure. 10. Subjects who had documented severe peripheral arterial occlusive disease defined as claudication with minimal exertion prior to the ablation procedure. 11. Subjects with history of renal failure requiring dialysis or hepatic failure prior to the ablation procedure. 12. A known drug and/or alcohol addiction. 13. Mental impairment or other conditions which may not allow the subject to understand the nature, significance, and scope of the study. 14. Subjects who are pregnant. 15. Subjects who had preoperative need for mechanical circulatory support or intravenous inotropes.

	16. Subjects who are on anti-arrhythmic drug therapy for the treatment of another arrhythmia. 17. Subjects in currently undergoing chemotherapy. 18. Subjects on long term treatment with oral or injected steroids (not including intermittent use of inhaled steroids for respiratory diseases). 19. Subjects who had known connective tissue disorders at the time of index ablation procedure. 20. Subjects who had known hypertrophic obstructive cardiomyopathy at the time of index ablation procedure. 21. Subjects with known cold agglutinin. 22. Subjects who had or tested positive for COVID-19. 23. Subjects with bleeding disorders and/or inability to receive anticoagulation 24. Subjects undergoing aortic dissection surgery as index procedure. 25. Cardiac surgical re-intervention since the index cardiac surgery with concomitant AF ablation procedure.
Subject Follow-up	Treated subjects will be assessed for primary safety through 30-days post-procedure. Primary performance will be assessed at at least 12-months post-procedure. The minimum follow-up window will be at 12-months, with a maximum follow-up window at 24-months.
Primary Endpoint(s)	<u>Primary Safety Endpoint:</u> The composite safety endpoint includes surgical ablation procedure related to death, stroke (regardless of level of disability), myocardial infarction, and major bleeding events within 30-days of the index ablation procedure. Deaths beyond 30-days and through last follow up that are attributed to surgical ablation procedure or CRYOF will also be reported as MAEs. The reported events will be adjudicated by an independent physician for severity and relatedness to device and/or procedure. <u>Primary Performance Endpoint:</u> The primary performance endpoint is freedom from any documented atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) lasting >30 seconds in duration at the last follow-up visit in the absence of Class I or III AADs (with the exception of AADs at doses not exceeding those previously failed). The rhythm status used for evaluation of this endpoint will be derived from a 24-hours electrocardiographic rhythm monitoring. The minimum follow-up window is 12 months and maximum at 24 months. Any of the following scenarios will be captured and reported as failure of this effectiveness endpoint: • Any electrocardiographically documented AF, AFL or AT recurrences lasting >30 seconds in duration at the last follow-up visit (by 30 second 12-lead ECG or 24-hours continuous ECG monitoring);

	• The use of either new Class I or III antiarrhythmic drugs or doses exceeding previously failed (i.e. prior to ablation) at the last follow-up visit; • Any subsequent catheter ablation or surgical ablation treatment for AF, AFL or AT following the index surgical AF ablation procedure (except for treatment of right typical atrial flutter).
Secondary Endpoints	Performance: 1. Freedom from any documented AF, AFL, or AT lasting >30 seconds at the last follow-up visit regardless of Class I or III AADs. 2. Freedom from any documented AF, AFL, or AT lasting >30 seconds at the last follow-up visit in the absence of Class I or III AADs. 3. Acute procedural success defined as documentation of sinus rhythm at the end of the procedure. Safety: 1. Implantation of a permanent pacemaker through last follow-up if related to the device or surgical ablation procedure. 2. Overall device or surgical ablation procedure related SAEs through last follow up.

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COMPLIANCE STATEMENT

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812 and OUS ISO14155:2020) 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.

This clinical investigation will be financed by AtriCure. Investigational sites will be compensated by AtriCure for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

1 INTRODUCTION

This clinical investigation will be conducted in accordance with this Clinical Investigational Plan (CIP), also referred to herein as the "Protocol". All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and the training will be documented appropriately. The investigator 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 will also determine the cause and implement appropriate corrective and preventative actions to address any significant noncompliance.

1.1 Background and Rationale

1.1.1 Background

Atrial Fibrillation (AF) is characterized by very fast, irregular beating of the heart's upper chambers (the atria). It occurs when normal sinus rhythm is disrupted by errant irregular electrical signals in the atria. These erratic electrical propagation patterns disrupt the regular pumping action of the atria, preventing complete filling of the ventricles, and causing irregular beating of the ventricles. These spasms often lead to regions of static blood flow in the atria and consequently, blood clot formation, stroke and even death. It is estimated that AF is responsible for 15% - 25% of all strokes. Symptoms of AF typically include a rapid and irregular heartbeat, palpitations, dyspnea, discomfort, dizziness and fatigue.

Atrial fibrillation (AF) is a common heart arrhythmia that carries a significant mortality and morbidity risk and is associated with three primary clinical sequelae: loss of atrial transport, loss of regular cardiac chamber synchronization, rhythm & rate response, and thromboembolism. Up to a third of all patients with symptomatic long-standing persistent AF will experience at least one embolic episode during the course of their atrial fibrillation. Lone AF (e.g. no structural heart disease) with no left atrial enlargement may be categorized as a benign disease since it is not associated with an increase in mortality or complications than that of the general population. However, AF patients, especially those with enlarged atria or structural heart disease, are at an increased risk of congestive heart failure, thromboembolic events, and mortality. In fact, permanent AF (long-standing persistent AF after the decision not to treat) is associated with 8.2% annual all-cause mortality, 5.1% annual thromboembolic event rate, 2.7% annual major bleeding rate, and 16.6% annual heart failure rate.[ii]

The underlying theory surrounding the source of irregular conduction pathways in patients with atrial fibrillation involves ectopic electrical activity or micro-reentrant circuits that can originate from specific locations in the heart such as the pulmonary vein orifice in patients with lone AF (focal), or more commonly associated with the reentry of conduction circuits throughout the atria in patients with structural remodeling (wavelet AF).

Only 12% of patients have Lone AF, leaving the remaining 88% with some form of structural heart disease.[iii] This structural heart disease commonly includes hypertension, coronary artery and valvular heart disease. Left untreated, AF can lead to ventricular dysfunction, atrial dysfunction, left atrial enlargement thus perpetuating the structural remodeling that causes and worsens atrial fibrillation and heart failure.[iv]

The relationship between progressive structural remodeling and atrial fibrillation explains why 88% of AF patients are persistent or permanent leaving only 12% as paroxysmal.[v] Furthermore, 76% of AF patients either have enlarged atria with diameter greater than 4.5 cm or an increase in left ventricular thickness.[vi] Atrial enlargement, as well as structural remodeling, determines the

incidence of atrial fibrillation and whether AF patients observe complications throughout their lifetime.

Patients newly diagnosed with AF are medically managed with multiple courses of antiarrhythmic drugs (AAD), and anticoagulants to lessen the risk of thromboembolic accidents. Within 5 years, most patients will become refractory to AADs, and will require additional intervention. Often AADs will have the effect of "dumbing down" the heart's natural pacemaker, necessitating the need for permanent rate control. Although the risk of thromboembolism is reduced in the presence of anticoagulation, it is still substantially higher than that observed in the general population. In addition, bleeding complications from anticoagulation regimens occur at a cumulative rate of 1% per year.

1.1.2 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) 2017 AF expert consensus statement[viii] 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.

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.[vii]

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

1.1.3 Atrial Fibrillation Treatment

AF is typically first treated with drug therapy, with an approximately equal split between rate and rhythm control drugs as first line of treatment. Recent large-scale studies have failed to show superiority of one treatment approach - rate or rhythm control - over another. Regardless of rate or rhythm control, continuous anticoagulation therapy is crucial in AF patients for stroke prevention. The AFFIRM study concluded that the benefit of restoring sinus rhythm in the rhythm control group was reversed by the toxicity of the antiarrhythmic drugs and hypothesized that if a treatment was available to restore sinus rhythm without the toxicity of antiarrhythmic drugs, survival may be improved.

Drug therapy failure may be due to either a lack of medication efficacy and/or a patient's inability to tolerate medications known to have serious and bothersome side effects, including those resulting from interactions with other drugs. According to its package insert, Cordarone® (amiodarone), the most widely prescribed anti-arrhythmic medication (not approved for the treatment of AF), is discontinued in 7-18% of patients due to intolerable side effects.

Surgical treatment of AF is usually considered when a patient is already scheduled for a concomitant cardiac procedure requiring access to the thoracic cavity. When performed concomitantly, the surgical treatment of AF is often performed using cardiopulmonary bypass on an open and arrested heart. The surgeon is unable to observe atrial function and cannot confirm treatment success intraoperatively because the atria must be beating in order to place a pacing electrode and confirm conduction block.

The Maze procedures (and its derivatives, Maze III, etc.), are considered the comparative standard for the effective treatment of AF. The Maze III procedure requires stopping the heart and then surgically cutting and re-sewing the atria to create a complex pattern of lesions throughout the atria that are intended to block macro-reentry circuits within the atria. In the intervening years, the Maze III procedure has been modified, but it remains the standard for treatment of atrial fibrillation. However, associated procedural mortality (2 to 10%) and morbidity including permanent pacemaker requirements (~15% of patients) have hindered the adoption of "cut and sew" procedure.

There have been many attempts to move away from the complexity and risk of the cut and sew Maze III procedure. Most of the effort has focused on procedures to isolate errant conduction signals that are suspected to originate from the pulmonary veins either by segmental ostial ablation or by the creation of a box lesion around the pulmonary veins. Electrically isolating the pulmonary veins may be effective for focal AF patients who have paroxysmal AF with no structural heart disease. However, more complex types of AF require a more comprehensive lesion pattern to block all reentrant circuits, and therefore sole isolation of the pulmonary veins is not an effective treatment.

To date, a percutaneous catheter-based or minimally invasive surgical procedure that can effectively and safely treat symptomatic longstanding persistent Atrial Fibrillation (AF) is unavailable.

The ideal treatment for AF would mitigate the detrimental sequelae of AF; that is, the procedure would restore normal sinus rhythm and cardiac hemodynamics, prevent continued remodeling and enlargement of the atria, and reduce the risk of thromboembolism. The ideal procedure would provide a means for assessing completeness of the lesion patterns. Continuous and complete lesions created throughout the atria and electrically silencing the posterior left atrium as well as isolating the pulmonary veins are most likely to prevent propagation of electrical signals capable of inducing and/or maintaining AF and prevent development of new reentrant circuits or atrial enlargement. The ideal procedure would also be performed utilizing minimally invasive, closed chest techniques.

1.1.4 Cryoablation

Cryosurgical ablation is defined as the use of a certain temperature below freezing to obtain a specific tissue response. The severity of the tissue response and destruction is directly related to the intensity of the freezing temperature. The mechanism of action of the use of freezing temperatures is that there is direct cell necrosis and vascular stasis which occurs only during the thawing period. The 4 stages are[ix]

1. Acute intracellular freezing and cell necrosis.
2. Vascular stasis.
3. Dehydration in the thawing period via osmosis due to ion imbalance between intracellular and extracellular fluid.
4. Finally, latent apoptosis which takes several days longer and can last for days.

The major advantages of cryothermy are: 1) visual confirmation of trans-murality by "ice ball" formation; 2) rapid creation of focal lesion; and 3) low risk of injury to adjacent tissues.[x]

1.1.5 Rationale for Conducting this Clinical Investigation

This study is proposed herein is to gather clinical data on the safety and performance of the CRYOF device used in concomitant cardiac procedures.

Specifically, data from this study will be used for submission to regulatory authorities in Europe, China and other geographies as needed.

2 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

The primary objective of this study is to evaluate the safety and performance of the CRYOF device. The performance of the device will be demonstrated by establishing that the device effectively eliminates persistent and long-standing persistent atrial fibrillation in a clinically significant proportion of treated patients.

Treated subjects will be assessed for primary safety through 30-days post-procedure. Primary performance will be assessed at least through the 12-months post-procedure visit.

The minimum follow-up window will be at 12-months, with a maximum follow-up window at 24-months.

2.2 Investigational Device(s) To Be Used in the Clinical Investigation

The subject device for this study will be the AtriCure cryoICE cryoablation system, which has been cleared under the 510 (k) process by the FDA and is approved in the UK and EU for commercial use. It is therefore not an investigational device.

The AtriCure cryoICE cryoablation system is comprised of:

- cryoICE® cryoFORM™ cryoablation probe, CRYOF
- AtriCure® Cryo Module (ACM1/ACM2)

2.2.1 Name of the Device(s) Under Investigation

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

2.2.2 Indication for Use

The AtriCure cryoICE cryoFORM cryoablation probe is indicated for use in the cryosurgical treatment of cardiac arrhythmias by freezing target tissues, creating an inflammatory response (cryonecrosis) that blocks the electrical conduction pathway.

2.2.3 Description of the Device(s) Under Investigation

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

2.2.4 Device Handling

Subjects enrolled in this study will already have been treated, therefore device accountability is not required.

3 CLINICAL INVESTIGATION DESIGN

This is a retrospective-prospective, multi-center, non-randomized, unblinded, post-market study sponsored by AtriCure, Inc. This study will be conducted in the US, UK, and/or EU 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.

The PIs at the sites are cardiac surgeons, qualified by education, experience, and training to assume responsibility for the conduct of this study. Up to 20 sites will participate in the study.

Up to 150 subjects will be enrolled as part of the study. Treated subjects will be assessed for primary safety through 30-days post-procedure. Primary performance will be assessed at at least 12-months post-procedure.

The minimum follow-up window will be at 12-months, with a maximum follow-up window at 24-months.

An independent Core Lab will be utilized for evaluation of the rhythm assessments. All assessments shall be performed in accordance with the core laboratory's recommended protocol which is provided to the sites in the Study Reference Manual.

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.

Adverse Events and medical device quality problems (for medical devices used during the procedure), including potential and actual device-related adverse events, certain malfunctions and user 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.

Critical decisions related to the design and execution of the study will be managed by a Study Oversight Committee.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this protocol for details.

3.1 Clinical Investigation Procedures and Follow-up Schedule

Clinical investigation sites that have treated subjects with the CRYOF surgical ablation system will be approached to determine if they are resourced and willing to consent subjects treated within the past 24-months post procedure for rhythm assessment via 24-hr rhythm monitoring.

The goal of this study is to collect data for patients in which the CRYOF device was used to produce a set of lesions that are based upon the standard Cox-Maze III lesion set (hereinafter referred to as “the optimum lesion set”), consisting of the following lesions:

Right Atrial lesion set

Lesion	Endo/Epi	Device(s)	Minimum Duration
Atriotomy, extending from RA free wall near AV grove, to between SVC and IVC	Endo	NA	NA
Posterior RA, from midway between SVC-IVC up to the orifice of the SVC	Endo	CRYOF	2 min
Inferior lateral RA, from midway between SVC-IVC down to the orifice of the IVC	Endo	CRYOF	2 min
Extend T lesion down to posterior-lateral tricuspid annulus	Endo	CRYOF	2 min
Lesion from RAA to tricuspid valve annulus (10 o’clock)	Endo	CRYOF	2 min

Left Atrial lesion set

Lesion	Endo/Epi	Device(s)	Minimum Duration
Posterior inferior wall of the LA encircling left inferior pulmonary vein	Endo	CRYOF	2 min
Posterior superior wall of LA encircling left superior pulmonary vein	Endo	CRYOF	2 min
From the wall of LA to posterior mitral valve annulus	Endo	CRYOF	2 min
From LAA orifice to left pulmonary veins	Endo	CRYOF	2 min

Coronary Sinus lesion

Lesion	Endo/Epi	Device(s)	Minimum Duration
Epicardial lesion down to the level of mitral valve annulus with the inclusion of coronary sinus. ***Ensure removal of retrograde cannula prior to lesion*	Epi	CRYOF	2 min

If, for whatever reason, not all above mentioned lesions were performed, data will be collected on the actual lesions performed in order to allow subgroup analysis of patients that received the optimum lesion set, against patient that received a sub-optimum lesion set.

The LAA, however, should have been managed/excluded in all subjects ideally using the AtriCure AtriClip ACH1, ACH2, or FLEX V devices. Suture techniques are allowed as well.

The follow-up assessment data will be entered into the EDC developed for the study.

Documentation and reason for screen failure (i.e., inability to consent, refused consent, did not meet inclusion exclusion criteria, death or major morbidity (such as stroke) etc.) will be secured on a screening log within the EDC.

3.2 Measures Taken to Avoid and Minimize Bias

This is a single-arm study. All enrolled subjects would have had a surgical ablation with the CRYOF device. Study data will be monitored against relevant source documents. An independent physician will adjudicate the SAEs reported in the study and rhythm assessments will also be adjudicated by a core lab. Furthermore, to mitigate temporal bias, enrollment in the trial will be based on random selection of treated subjects. The sequence with which treated subjects will be invited to participate in the trial will be randomly generated by the sponsor and provided to each site.

3.3 Suspension or Early Termination of the Clinical Investigation

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
- A Study Oversight Committee (e.g., National PI(s) & AtriCure Medical Advisor) makes a recommendation to stop or terminate the clinical investigation.

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. All applicable clinical investigation documents shall be subject to the same retention policy as detailed in [Section 11.5] of the 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 Trial Agreement.

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

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

4 ENDPOINTS

4.1 Primary Safety Endpoint

This composite safety endpoint includes surgical ablation procedure related to death, stroke (regardless of level of disability), myocardial infarction, and major bleeding events within 30-days of the index ablation procedure. Deaths beyond 30-days and through last follow up that are attributed to surgical ablation procedure or CRYOF would be reported as Major Adverse Events (MAEs).

All MAEs will be adjudicated by an independent physician, thus maintaining the objectivity of the primary safety endpoint. A detailed definition of the MAEs is provided below:

- Excessive Bleeding: is defined as a major complication if it is subsequent to a device related or study procedure-related injury and is treated with transfusion or results in a 20% or greater fall in HCT. Transfusion for anemia or other pre-existing condition that cause a fall in HCT without acute bleeding will not be considered a Major Adverse Event. Documentation of the cause of the bleed, and transfusion, and/or 20% or greater drop in HCT.

- Myocardial infarction (MI): When low blood flow causes the heart to starve for oxygen. Heart muscle dies or becomes permanently damaged. Documentation of MI; 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 persist for more than 1 hr, (2) development of new pathological Q waves on an ECG, and (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- Stroke: A stroke is an interruption of the blood supply to any part of the brain. 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 a focal or global neurological deficit ≥24 h; OR <24 h if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death AND no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Diagnosis should be confirmed by a neurology or neurosurgical specialist utilizing a neuroimaging procedure (MR or CT scan or cerebral angiography) or lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage). Documentation of a stroke or CVA consisting of acute loss of neurological function caused by an ischemic event with residual symptoms at least 24 hours after onset confirmed by CT or MRI scan or cerebral angiography of acute neurological event.

- Transient Ischemic attacks (TIA): A transient ischemic attack is a "mini-stroke" caused by Temporary disturbance of blood supply to an area of the brain, which results in a sudden, brief decrease in brain function. Clinical symptoms similar to stroke but last for less than 24 hours. Documentation of TIA neuroimaging without tissue injury consistent with acute loss of neurological function caused by an ischemic event with resolution of symptoms within 24 hours after onset.

- Death: Document cause of death and include autopsy findings if autopsy performed.

4.2 Primary Performance Endpoint

The primary performance endpoint is defined as freedom from any documented AF, AFL, or AT lasting >30 seconds at the last 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 results of the 24-Hour electrocardiographic rhythm monitoring data used for the primary performance endpoint, will be evaluated by an independent core lab thus maintaining objectivity of the primary performance endpoint.

Subjects will be considered primary performance failures if any of the following conditions are observed:

- Any electrocardiographically documented AF, AFL or AT recurrences lasting >30 seconds in duration at the last follow-up visit (by 30 second 12-lead ECG or 24-hours continuous ECG monitoring);
- The use of either new Class I or III antiarrhythmic drugs or doses exceeding previously failed (i.e., prior to ablation) at the last follow-up visit;
- Any subsequent catheter ablation or surgical ablation treatment for AF, AFL or AT following the index surgical AF ablation procedure (except for treatment of right typical atrial flutter).

4.3 Secondary Safety Endpoint

Key Secondary Safety Endpoints include:

- Implantation of a permanent pacemaker post-procedure through the last follow-up period.
- Overall device or surgical ablation procedure related SAEs through last follow up.

4.4 Secondary Performance Endpoint

Key Secondary Performance Endpoints include:

- Freedom from any documented AF, AFL, or AT lasting >30 seconds at the last follow-up visit regardless of Class I or III AADs.
- Freedom from any documented AF, AFL, or AT lasting >30 seconds at the last follow-up visit absent of Class I or III AADs.
- Acute procedural success defined as documentation of sinus rhythm at the end of the procedure.

4.5 Descriptive Endpoint(s) or Additional Data

If necessary, additional analyses and endpoints will be defined in a separate Statistical Analysis Plan (SAP) prior to database lock.

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll patients who have undergone concomitant surgical AF ablation using the CRYOF device. Subjects must meet all eligibility criteria and provide written informed consent prior to collection of study data.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Potential subjects presenting at the clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in [Section 5.2.2]).

Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the protocol, and if applicable will be entered into a site-specific screening log.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical

investigation personnel will record the reasons for screen failure (e.g. inability to consent, refusal to consent, did not meeting inclusion/exclusion criteria, death or major morbidity (such as stroke) etc.) on a screening log within the EDC as required.

Subjects meeting general inclusion criteria and no exclusion criteria will be asked to sign an Informed Consent form if they wish to participate in the clinical investigation. These subjects will also be entered into the screening log.

Subject data will be collected following enrollment into the clinical investigation and will be based on random selection of treated subjects.

5.2.2 Informed Consent

The Informed Consent Form (ICF) must have the approval of the IRB or favorable opinion of the EC. While some institutions may request 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 ISO 14155:2020 and is approved by the Sponsor.

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

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

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

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

The ICF will clearly stipulate that the duration of the study is approximately 1.5 years, and the implications of this commitment will be reviewed and discussed with the subjects prior to enrollment in the study.

5.2.2.1 Special Circumstances for Informed Consent

For eligible subjects in the U.S., an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally acceptable representative.

For subjects outside of the U.S. (OUS), a separate GDPR consent may be required if not already included within the ICF.

In addition,

- Individuals under the age of 18 or age of legal consent are excluded from the study population.
- Pregnant or breastfeeding women are excluded from the study population.

Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population.

For individuals unable to read or write Informed consent will be obtained through a supervised oral process. An independent witness will be present throughout the Informed Consent process. The written Informed Consent form and any other information will be read aloud and explained to the prospective subject or his/her legally acceptable representative and either will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained, and that informed consent was freely given.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records at the site and interview with a candidate subject. Subjects must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the subject is excluded from the clinical investigation and cannot be enrolled.

5.3.2 Inclusion Criteria

5.3.2.1 General Inclusion Criteria

All subjects recruited for study participation must meet all of the following inclusion criteria to be enrolled in the study:

1. Subject is greater than or equal to 18 years of age.
2. Subject has documented history of atrial fibrillation.
3. Subjects who received surgical ablation for their atrial fibrillation using CRYOF and on whom at least the following lesions were performed: left and right pulmonary vein isolation, roof and floor lines, mitral annulus line, a connecting lesion from left atrial appendage to left pulmonary vein, coronary sinus lesion, and LAA exclusion, with a lesion duration of at least 2 minutes.
4. Stable subject that underwent non-emergent cardiac surgical procedure(s) on cardiopulmonary bypass including open-heart surgery for one or more of the

following: mitral valve repair or replacement, aortic valve repair or replacement, tricuspid valve repair or replacement, and coronary artery bypass procedures, or atrial septal defect (ASD) repair.

5. Left Ventricular Ejection Fraction ≥ 30% (determined by echocardiography or cardiac catheterization performed within 90 days of enrollment as documented in subject medical history).
6. Subject is willing and able to provide written informed consent.
7. Subject is willing and able to return for scheduled follow-up visits.

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

Potential subjects required for study participation must not meet any of the following exclusion criteria to be enrolled in the study:

1. Stand-alone AF without indication(s) for concomitant CABG and/or valve surgery.
2. Previous left sided ablation procedures prior to surgical ablation.
3. Untreated atrial flutter and symptomatic ventricular arrythmia.
4. Known carotid artery stenosis greater than 80% prior to index ablation procedure.
5. Prior history of ischemic stroke or hemorrhagic stroke.
6. History of MI with ST elevation within 6 weeks prior to the index ablation
7. Documented AF duration of greater than 10 years.
8. Large left atrial size i.e., LA diameter >7 cm prior to the index ablation procedure.
9. Subjects with active systemic infection prior to index ablation procedure.
10. Subjects who had documented severe peripheral arterial occlusive disease defined as claudication with minimal exertion prior to the ablation procedure.
11. Subjects with history of renal failure requiring dialysis or hepatic failure prior to the ablation procedure.
12. A known drug and/or alcohol addiction.
13. Mental impairment or other conditions which may not allow the subject to understand the nature, significance, and scope of the study.
14. Subjects who are pregnant.
15. Subjects who had preoperative need for mechanical circulatory support or intravenous inotropes.
16. Subjects who are on anti-arrhythmic drug therapy for the treatment of another arrhythmia.
17. Subjects in currently undergoing chemotherapy.
18. Subjects on long term treatment with oral or injected steroids (not including intermittent use of inhaled steroids for respiratory diseases).
19. Subjects who had known connective tissue disorders at the time of index ablation procedure.
20. Subjects who had known hypertrophic obstructive cardiomyopathy at the time of index ablation procedure.
21. Subjects with known cold agglutinin.
22. Subjects who had or tested positive for COVID-19.
23. Subjects with bleeding disorders and/or inability to receive anticoagulation
24. Subjects undergoing aortic dissection surgery as index procedure.
25. Cardiac surgical re-intervention since the index cardiac surgery with concomitant AF ablation procedure.

5.4 Subject Enrollment

Subjects will be provided the IRB/EC approved ICFs and will have the opportunity to read, understand, and have their questions answered prior to signing the ICFs. If the subject agrees to participate in the study and signs consent, the ICF process will be completed. The subject must sign and date the ICF prior to collection of study data. The person reviewing the ICF with the subject will also sign and date the ICFs. The subject will be given copies of the signed ICFs to keep.

Upon entering subject enrollment information into Clindex, each subject will be assigned a unique identification (ID) number sequentially in ascending order. All subjects who sign the ICFs will be documented in a Screening and Enrollment Log. For subjects who sign the ICF but are ineligible to participate, minimum baseline characteristics: age, gender, race, screening date and screen failure reason (s) will be captured in Clindex.

A subject is considered enrolled in the clinical investigation from the moment the subject provides written informed consent and has been confirmed to meet all inclusion criteria and none of the exclusion criteria.

5.4.1 Historically Under-Represented Demographic Subgroups

AtriCure will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- as appropriate and necessary, AtriCure will train sites on the importance of recruiting and retaining subjects in the clinical investigation
- approach sites without bias or consideration for specific demographic subgroups
- have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials.

5.5 Subject Withdrawal

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

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated due to site/study termination

The Sponsor must be notified by the site of the reason(s) for subject discontinuation and record a reason for termination in the case report form (CRF). Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

<u>Investigator Decision</u>

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

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

If the subject misses their scheduled follow-up and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall

make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified if applicable) should be sent to the subject.

Withdrawal of consent
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 the 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).

Other (which may include)

- Protocol deviation, noncompliance, or violation;
- Investigator/Sponsor recommendation;

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. No additional follow–up will be required or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive). The investigator can use existing data and ask for the subject's permission to collect follow-up data about his/her status/condition including information about device clinical performance or safety. If permission is obtained, the relevant data shall be included in the clinical investigation report.

5.6 Number of Subjects

Up to 150 subjects will be enrolled at up to 20 sites in the US, UK and/or EU.

5.7 Total Expected Duration of the Clinical Investigation

The expected duration of the study is approximately 21 months. Enrollment will be closely monitored and AtriCure will work directly with the sites to clearly understand the enrollment challenges they might be facing, retrain as needed and pursue other strategies to redress any enrollment lapse. Subjects will be exited from the trial at the conclusion of their primary performance follow-up visit occurring at least 12-months post-procedure.

6 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Study Eligibility

All subjects recruited for study enrollment must meet all study enrollment criteria prior to being enrolled in the study. The clinical investigation site will review all subjects treated with the CRYOF surgical ablation system, and who are within 24-months post-procedure for study eligibility. Once the initial chart review indicates that the subject meets the study inclusion / exclusion criteria, the subject will be approached for their interest in the study, including willingness to return for their follow-up visit.

6.2 Follow-up Assessments

6.2.1 12-Month Visit (≥ 12-months but ≤ 24-months post index ablation procedure)

Subjects will be consented 12 to 24 months post procedure and will be provided with a 24-Hour rhythm monitoring device at that time. The post procedure follow-up assessment will include:

- NYHA Classification
- 24-Hr Rhythm Assessment
- Evaluation of AEs/SAEs
- Medications – class I and III AAD's and anticoagulants, including any adjustments
- Review cardioversion since last visit

Note: If a clinical site is capable of remote subject visits, a modified visit assessment may be conducted. Remote subject visits should include Telemedicine appointments with the Investigator, where feasible, to allow direct engagement with the study subject and to ensure complete data collection. Rhythm monitoring devices may be provided to the subject either during an in-clinic follow-up visit, or shipped to the subject for a remote follow-up visit as applicable.

If clinical site is NOT able to perform remote subject visits, an attempt will be made to schedule the study subject visit as close to the visit window as is possible.

Regardless of when the subject is consented, the following data will be collected by reviewing the subjects' medical records retrospectively. For retrospective visits that fall outside of the required windows, please refer to sections 6.2.9 (Unscheduled Visit) and 10.6 (Protocol Deviations).

6.2.2 Baseline (within 30 days of index ablation procedure)

- Inclusion/Exclusion criteria
- Demographic information (Age, Sex, Race, Ethnicity)
- Review of Medical and Cardiac history, including AF history
- Documentation of AF classification (Persistent or Longstanding Persistent)
- Vital History (Height, Weight, BMI, Blood Pressure, Heart Rate)
- NYHA Classification
- Heart Rhythm Assessment using 12 Lead ECG, if done
- ECHO (TTE) within 90 days of the procedure, if done
- Medications history – Antiarrhythmic drugs (AADs), anticoagulants including previous AAD treatment failures. Medication information should include:
    - Name and indication
    - Dosage with units and frequency
    - Start and stop dates

6.2.3 Surgical Procedure

- Evaluation of adverse events (AEs)/SAEs
- Cox-Maze III
- Con-concomitant surgical procedure
- Post-procedure heart rhythm assessment using 12 lead ECG, if done
- Cardioversion history, if applicable

6.2.4 Pre-Discharge

- Evaluation of any AEs/SAEs
- Heart Rhythm Assessment using 12 lead ECG, if done
- Medications – class I and III AAD's and anticoagulants, including any adjustments
- Cardioversion history since procedure

Medication review *Note: Medications administered during the post-operative period do not need to be captured in the eCRF.

6.2.5 30-days Post-Procedure (+/- 7 days)

- NYHA Classification
- Heart Rhythm Assessment using 12 lead ECG, if done
- Evaluation of any AEs/SAEs
- Medications – class I and III AAD's and anticoagulants, including any adjustments
- Review cardioversion since last visit

6.2.6 Study Exit

Once study subjects have completed their last follow-up visit, and 24-Hr rhythm assessment has been obtained, the subject will be exited from the study.

6.2.7 Unscheduled Visit(s)

An unscheduled visit is defined as a visit that occurs outside of the defined visit windows. Subjects reporting symptoms of AF/AFL/AT prior to their last follow-up visit, should contact their site for an in-clinic or remote evaluation. The following will be conducted/collected at the visit:

- Heart Rhythm Assessment using 12 lead ECG or equivalent per standard of care, if done
- Any AF treatment that was needed
- Evaluation of any AEs/SAEs
- Medications – class I and III AADs and anticoagulants, including any adjustments

6.2.8 Schedule of Events

Trial Activity	Visit 1 Baseline (Within 30 days of index procedure)	Visit 2 Procedure	Visit 3 Pre-Discharge	Visit 4 30-days (Within 23-37 days of index procedure)	Visit 5 12-months (≥ 12-months but ≤ 24-months of index ablation procedure)	 Unscheduled visit
Informed consent & Inclusion/Exclusion	X					
Demographics	X					
Medical/Surgical History	X					
AF Classification	X					
Vital History	X					
NYHA Classification	X			X	X	X
12 Lead ECG, if done[1]	X	X	X	X		X
Medications/AAD Adjustment Review[2]	X		X	X	X	X
Adverse Events (AEs/SAEs)		X	X	X	X	X
Echocardiogram (transthoracic), if done	X					
Cox Maze III		X				
Concomitant Surgical Procedure		X				
Cardioversion Review[3]		X	X	X	X	X
24-Hours Holter (or equivalent)					X	

[1] 12-lead ECG performed will need to be 30 seconds in length.
[2] Class I/III AADs and/or OACs only
[3] At physician's discretion and per institutions Standard of Care (SOC).

6.3 Requirement for Clinical Laboratories

An independent core laboratory will be utilized for assessment of the following data collected on subjects:

- 24-Hour rhythm monitoring recordings

All monitoring shall be performed in accordance with the core laboratory's recommended protocol.

7 ADVERSE EVENTS

Safety data for the primary safety endpoint will be collected from the start of the index ablation procedure to 30-days post procedure. The primary safety endpoint will be an evaluation of the incidence of major adverse events (MAEs) listed in section 4.1 for the procedural to 30-day post procedure time period. Deaths beyond 30-days or through last follow-up that are attributed to the surgical ablation procedure or CRYOF would be reported as MAEs.

7.1 Definition

7.1.1 Major Adverse Event

Events qualifying as MAEs as defined in section 4.1 include:

- Excessive bleeding
- Myocardial Infarction (MI)
- Stroke, TIA
- Death

Any condition that was records as pre-existing is not a MAE unless there is a change in the nature, severity, or degree of the condition.

Sick Sinus Syndrome (SSS) and the implantation of a pacemaker for treatment of SSS post procedure will not be recorded as a MAE since it is a known underlying condition for subjects with long-standing persistent AF undergoing cardiac coagulation procedures.

7.1.2 Adverse Event

Adverse Event (AE) is defined as any undesirable clinical occurrence or change from subject's baseline (or pre-device procedure) condition, whether it is considered device related or not. An AE is also defined by the International Organization for Standardization (ISO) as an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Adverse Event Identification: a condition that is one of the following:

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

7.1.3 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a Serious Adverse Event (SAE).

a) Led to a death,
b) Led to a serious deterioration in health of the subject, that either resulted in
    1. Life-threatening illness or injury, or
    2. Hospitalization (initial or prolonged) or
    3. Disability or permanent impairment of a body structure or a body function
    4. Congenital anomaly (physical or mental)/birth defect/fetal distress/fetal death
    5. Chronic disease
    6. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c) Other Serious (important Medical Events).

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

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.

7.1.4 Device Deficiency/Device Malfunction

Device Deficiency is defined as an inadequacy of a medical device related to its identity, quality, usability, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: Performance specifications include all claims made in the labeling of the device.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended.

All device deficiencies of the CRYOF device shall be documented throughout the clinical investigation and managed by the sponsor in accordance with written procedures for the control of a non-conforming product. The sponsor shall take, where applicable, appropriate corrective and preventative actions to protect the safety of subjects, users, and other persons. Device deficiencies of the comparator, if applicable, shall be documented. Where applicable, the analysis of used or explanted investigational devices shall be included as supportive information.

7.2 Pre-Existing Conditions Versus Adverse Events

A pre-existing condition is defined as a medical condition that is present before the index ablation procedure 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 CRF as an exacerbation of the pre-existing condition and the start date will be recorded as the time when the exacerbation occurred.

7.3 Severity of Adverse Events

It is the Investigator's responsibility to assess the severity of an AE. 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/surgical intervention (including hospitalization or prolongation of hospitalization) required.

7.4 Device Relationship

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

It is the Investigator's responsibility to assess the relationship of an AE to the study procedure and/or device.

Adverse events will be assigned an attribution according to the Investigator's believed primary cause. Events will be categorized by relationship to the investigational device(s) listed in this protocol or ancillary device, surgical ablation procedure, general cardiac surgical procedure or subsequent intervention, concomitant medications, pre-existing condition, intercurrent condition, intercurrent intervention, or unknown.

The following guidelines should be used in determining the relationship of an adverse event to the study device or procedure:

- **Unknown:** A clinical event (including abnormal laboratory result) that cannot be determined to be related or unrelated to device/procedure/drug given information provided.
- **Device Related Adverse Event**: An adverse event, that in the judgment of the Investigator, resulted from use of the cryoICE® cryoablation system may have caused or contributed to the AE.
- **Procedure Related Adverse Event**: An adverse event which, in the judgment of the Investigator, results as a consequence of the investigational procedure and is not specifically related to the use of the cryoICE® cryoablation system.
- **General Surgery Related Adverse Event**: An adverse event which, in the judgement of the Investigator, results as a consequence of general cardiac surgical procedural complications and/or subsequent interventions.
- **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).
- **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.

7.4.1 Unanticipated (Serious Adverse) Device Effect [U(S)ADE]

Unanticipated serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or 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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.5 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.5.1 AE/ADE/UADE Reporting

General AE Reporting

Safety surveillance and reporting starts as soon as the subject is enrolled in the clinical investigation. Safety surveillance and reporting will continue until the 12-Month follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. All adverse event data, including deaths and device deficiency data, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Except for those events listed in Section 7.6, AEs potentially related to the study procedure or AtriCure devices used in the study and other AEs that the PI determines as critical to safety evaluation will be captured on the eCRF. Standard medical terminology should be used when recording AEs.

In addition, the following information should be recorded:

- Onset Date
- Resolution date or date of death
- Intensity of the event
- Action Taken
- Outcome of the event
- Relationship of AE
- Indication of whether the event is serious

7.5.2 SAE/USADE Reporting

The investigator (or designee) must report all SAE/USADEs to the Sponsor via the Adverse Event CRF as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 10 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined. An event determined by the Investigator to be life-threatening or to have led to death must be reported within 24 hours.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the eCRF and ensure relevant source documents are collected. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements. 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 report-ability 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 thirty (30) 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 device or procedure related 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.

7.5.3 Device Deficiency/Malfunction Reporting

All device deficiencies/malfunctions should be reported on the appropriate CRF.

The investigator should report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 10 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

7.5.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

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

Clinical investigation SAEs and device deficiencies/malfunctions reportable per MedDEV 2.7/3 regulations will be submitted to European Competent Authorities by the Sponsor's Clinical Product Safety & Surveillance Group.

7.6 Expected Morbidity/Procedural Complications Reporting

For purposes of this study, the following events occurring within 48 hours of study procedures are not considered reportable (not recorded on eCRF but recorded in source documents) as they are normally expected to occur in conjunction with surgical treatment for non-paroxysmal forms of atrial fibrillation procedures (Maze III) or are associated with customary, standard care of subjects undergoing cardiac surgery:

- Chest pain without associated ECG changes
- Post-operative/post-procedure pain
- Post-anesthesia emesis, nausea, or headache (within 24 hours of procedure)
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction
- Pre - planned future surgical procedures
- Low grade temperature increase (101°F or 38.5°C)
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo.
- Elevated white blood count, outside the standard laboratory normal value, without signs and symptoms of infection
- Post-operative hematocrit decreases 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.
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Any blood transfusions during preplanned operative procedures and unrelated to an adverse event.
- Thrombocytopenia: does not become an AE until treatment is administered.

- Atelectasis - collapse of lung tissue affecting part or all of one lung; the alveoli are deflated. This is not considered to be an AE unless treatment other than chest PT is required or it prolongs hospitalization.
- Hyperglycemia - The use of insulin in the post-operative period does not constitute hyperglycemia if during the same hospitalization. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post-operative does not constitute hyperglycemia.
- Pleural effusion is not an event unless treatment with thoracentesis or chest tube insertion is required
- Pericardial effusion without hemodynamic compromise or treatment
- Atrial Fibrillation /Atrial Flutter/Atrial Tachycardia with or without cardioversion.
- Junctional Rhythm requiring temporary pacing

Note: Treated subjects will have received 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.

Note: This listing of events is intended to provide guidance to the Investigator and 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 based on the IRB/EC reporting requirements or the subject clinical situation.

7.7 Product Complaints

A product complaint is any written electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability safety, or performance of a device after it is release for distribution (a medical device that has been released from the organization's control or related to a service that affects the performance of such medical devices). Product complaints may or may not be associated with an AE.

7.7.1 Reporting Product Complaints

All product complaints (as defined above) related to an investigational product (shall be documented throughout the clinical investigation and appropriately managed by the sponsor. All reported device observations, malfunctions or failures for the cryoICE® cryoablation system are required to be documented in the EDC within 10 days of observation of the Product Complaint and sent via e-mail to pcomplaints@atricure.com by the PI or study staff.

If the cryoICE® cryoablation system or component is involved in a complaint, the device should be returned to AtriCure (e.g., product is damaged or use results in an AE). If this occurs, sponsor representatives will send a Used Product Return Kit to study site personnel for packaging the product; which (depending on the product) may be sent to the appropriate facility for decontamination and further investigation of the complaint.

7.7.2 Reporting Product Complaints with Non-Investigational Device Products

All reported device observations, malfunctions or failures for AtriCure Non-Investigational (i.e. Marketed Products) are required to be documented in the Clindex database on the device observation eCRF and emailed to pcomplaints@atricure.com within 10 days of the observation by the PI or study staff.

If an event involving an AtriCure device is subject to reporting under the Medical Device Reporting Regulation (MDR), AtriCure shall submit to the FDA the appropriate reports required by MDR within the timeframes identified in 21 CFR Part 803.

7.7.3 Non-AtriCure Product Complaints

In compliance with the requirements of 21 CFR Part 803.30 (MDR), the study site (user facility) will 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.

7.7.4 Reporting Product Complaints for Global Compliance

If a Product Complaint is reported in conjunction with a SAE/UADE, reporting guidelines will be the same as those listed in Section 7.5.4.

8 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, pool-ability analyses, subgroup analyses, etc., may be maintained in a separate Statistical Analysis Plan.

8.1 Analysis Populations

Intention-to-Treat Population:
The Intention-to-Treat (ITT) population consists of the subjects on whom the CRYOF device was used. This is the primary population for performance and safety endpoints.

Protocol Population:
The Per-Protocol (PP) study population is defined by the ITT population but without any major protocol deviations, that is, those that could potentially bias the results. This population is defined for the primary performance endpoints.

8.2 Statistical Analyses

The primary goal of the study is to demonstrate safety and performance of the CRYOF device. For the study to be successful, both endpoints must be statistically significant relative to their respective performance goals.

Standard descriptive statistics will be used to summarize numeric variables, including the number of observed values, mean, standard deviation, median, minimum and maximum values. Summaries of categorical variables will include the number and percentage of observed values, at each level of the categorical variable. Baseline and demographic information, including age, gender, race, ethnicity, height, weight, BMI, and medical history will be summarized with standard descriptive statistics.

8.2.1 Primary Performance Endpoint Analysis

The primary performance endpoint is defined as freedom from any documented AF, AFL, or AT lasting >30 seconds at the last 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 primary performance endpoint is further defined in section 4.2 of the protocol.

Subjects meeting the primary performance endpoint will be labeled as “responders”, and the proportion of responders will be compared to a performance goal (PG) of 55%.

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

$$H_0: p \leq 0.55$$

$$H_A: p > 0.55$$

where *p* is the responder rate at last follow-up visit occurring at least 12-months post-procedure. The ITT population will be the primary population for this analysis.

8.2.2 Primary Safety Endpoint Analysis

The primary safety endpoint is the proportion of subjects free from MAEs, as described in section 4.1 of the protocol, through 30-days post-procedure. The MAE rate will be compared against a PG of 15%.

An exact binomial test will be conducted at a one-sided α = 0.05 level of significance to test the following hypothesis that the proportion of MAEs is significantly lower than the PG:

The hypothesis test for the safety endpoint is:

$$H_0: q \geq 0.15$$

$$H_A: q < 0.15$$

where *q* is the proportion of subjects with MAEs through 30-days post-procedure in the safety population. The ITT population will be the primary population for this analysis.

8.2.3 Secondary Safety and Performance Endpoint Analyses

The secondary safety and performance endpoints are described in section 4.3 and 4.4 of the protocol.

All analyses will be conducted using appropriate statistical methods. These will include analyses of the populations and subgroups as specified in this protocol and may also include additional endpoints, populations and/or subgroups.

8.3 Sample Size Calculation and Assumptions

Performance Endpoint

Based a PGI of 55% success and an expected success rate of 68%, a sample size of 140 subjects provides >88% power using a one-sided Exact test, with α = 0.025 level of significance to demonstrate primary performance success. Assuming an attrition rate of 6.5% at the last follow-up visit post-procedure, a total of 150 subjects will be enrolled.

The lowest primary performance endpoint that would meet the PG is 63.6% (that is, 89 out of 140 subjects are responders).

Safety Endpoint

Minimal to no missing data are expected for the primary safety endpoint. Based on a PG of 15%, and an expected population MAE rate of up to 8.5%, a sample size of 150 subjects will have 80% power using a one-sided Exact test, with at a one-sided $\alpha = 0.05$ level of significance.

The highest primary safety endpoint that would meet the PG would be 10% (that is, 15 out of 150 subjects experience at least one MAE).

8.4 Timing of Analysis

The primary performance endpoint analysis will be conducted when all subjects have completed at least their 12-months post-procedure visit. The expected duration of the study is approximately 21 months.

8.5 Subgroup Analysis

No subgroup analyses are planned for this clinical investigation. However primary safety and performance endpoints will be summarized by sex, race and other subgroups as needed.

8.6 Multiplicity

No alpha multiplicity adjustments are planned for the exploratory and supporting secondary endpoints and analysis populations defined in the study.

8.7 Pooling Strategy

For this study, data will be pooled from multiple study sites. The justification for pooling will be made on a clinical basis considering three factors: (1) the study sites must implement one common protocol, (2) the Sponsor must closely monitor study site compliance with the protocol, and (3) the study site must use common data collection procedures.

8.8 Procedures for Accounting for Missing Data

As applicable, several sensitivity analyses will be performed to evaluate the effect of the missing data on the primary performance and safety endpoints, including multiple imputation, last observation carried forward (LOCF) and a tipping point analysis. Details will be provided in the SAP prior to database lock.

8.9 Statistical Criteria for Termination

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

8.10 Success Criteria

For the trial to be successful, both performance and safety endpoints must be statistically significant relative to their respective performance goals and that both primary safety and performance hypotheses are met. If both the null effectiveness hypothesis and the null safety hypotheses are rejected, the treatment will be considered beneficial.

8.11 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

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

10.2 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by AtriCure. Investigational sites will be compensated by AtriCure for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

10.3 Protocol Amendments

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

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

The protocol and all subsequent amendments to the protocol are prepared by the Sponsor, agreed upon between the Sponsor and the National Principal Investigator, accepted by all Principal investigators, and are recorded with a justification for each amendment.

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the protocol requirements, investigational device usage, electronic case report form completion and clinical investigation personnel responsibilities.

All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any protocol-related activities that are not considered standard of care at the site.

10.5 Monitoring

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

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

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

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;
- The conduct of the study is in compliance with the currently approved protocol and amendment(s), applicable GCPs, and with applicable local and regional regulatory requirements.

10.6 Protocol Deviations

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

For retrospective data collection, it is possible that subject visits post-procedure will vary based on institutional standard of care. For the purposes of this study, any subject visit that falls outside of the protocol defined visit window will not be documented as a protocol deviation, and individual protocol deviation waivers will not be required. Additionally, NYHA classification, 12 lead ECG, and medication reviews that were not retrospectively performed will not be documented as a protocol deviation.

All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the protocol and regulatory requirements and dealt with according to written procedures.

Investigators will inform their IRB/EC or equivalent committee of all protocol deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

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

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

Repeated non-compliance with the signed agreement, the protocol or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the Investigator's participation in the clinical investigation.

10.7 Quality Assurance Audit

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

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

10.8 Committees

The sponsor shall ensure oversight of any clinical investigation-related duties and functions. The outsourcing of duties or functions to external organizations, including subcontractors of the sponsor's CRO(s)/Committees, shall be addressed by the sponsor in accordance with written procedures for control of suppliers and/or charters as applicable. Additionally, records of transfer of duties and functions shall be maintained where applicable.

10.8.1 Study Oversight Committee

The Study Oversight Committee is comprised of the National PI(s) and Sponsor Medical Advisor. The Chairman of the core laboratories and other sponsor personnel may also participate in the Committee meetings if appropriate. Meeting minutes from this committee will be filed with the sponsor.

The Study Oversight Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation.

Specifically, the committee with participate and/or advise on the following:

- Review of the study protocol
- Review of the training material for the sites as applicable
- Study operations and safety
- Discussion of study related issues with the sites, as needed

- Regulatory communication, as needed

10.8.2 Publications Committee

A Publication Committee may be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include the National PI(s), Site Principal Investigators, a representative of the Sponsor and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations.

10.8.3 Independent Physician Adjudicator (IPA)

An independent, non-investigator physician(s) will function as the adjudicator(s) under the direction of AtriCure, Inc. The physician(s) will be responsible for the review and adjudication of reported adverse events occurring up to 12-months post-procedure, including:

1. All Major Adverse Events listed under the primary safety endpoint;
2. All Serious Adverse Events;
3. All Unanticipated Device Effects;
4. All Adverse Events that are potentially related to the procedure or any of the AtriCure devices used in the study.

In addition, all primary safety endpoints and other adverse events determined by the adjudicator(s) to be relevant, will be adjudicated until the subject exits the study.

11 DATA HANDLING AND RECORD KEEPING

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

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

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

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

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

The investigator shall assure the accuracy, attribution, completeness, legibility and timelines of the data reported to the sponsor on the CRFs and in all required reports. All copies of the retained

original source documents shall be certified, as indicated by a dated signature by a member of the investigation site team unless generated through a validated process.

11.1 Protection of Personally Identifiable Information

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

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

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

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

11.2 Data Management Plan

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

11.3 Source Documentation

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

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, protocol number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, procedure/admission notes, relevant laboratory reports and

ECGs, including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.

11.4 Case Report Form Completion

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

CRF completion guidelines may also be developed to provide instructions to the site for accurate completion, correction and signature of CRFs along with expectations on handling clinical investigation deviations and unknown data, thus reducing the need of sponsor data queries. Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements.

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.

11.6 Investigational Devices Accountability

Subjects enrolled in this study will already have been treated, therefore device accountability is not required.

12 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

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

The IRB/EC may require a draft of the Clinical Study Agreement and proposed compensation to the investigation site or principal investigator be provided, including a letter of the sponsor confirming outsourcing of duties and functions and CVs of the investigational site team.

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

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

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

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

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. Note: National regulations can apply concerning the timing of registration or updating the contents.

13 CLINICAL INVESTIGATION CONCLUSION

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.

14 PUBLICATION POLICY

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

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

15 RISK ANALYSIS

Ablation procedures are commonly performed and are a well-accepted treatment for subjects with AF, with a well-established risk profile. The primary objective of this study is to evaluate the safety and performance of CRYOF device.

15.1 Anticipated Clinical 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.
- Overall advancement of medical and scientific knowledge that may benefit future subjects with similar conditions may be gained through this clinical study.

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

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Complications that could specifically have occurred at any time during the procedure, post procedure or may be possible during the follow-up period with the AtriCure cryoICE System include the following:

- Undetected incomplete lesion
- Non-transmural lesion
- Lateral lesion spread
- Ablation of unintended tissue
- Tissue perforation
- Phrenic nerve injury
- Nitrous Oxide exposure
- Tissue tear resulting in hemorrhage
- Procedure interruption or delay
- Pulmonary vein stenosis
- Cardiac tamponade

15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk/Quality Management Report

Subjects enrolled in this trial have already been treated, however risk analyses and evaluations of the device hazards and product design, application, and process have been conducted for the Cryo Ablation System devices.

Upon review of the risk documentation for the Cryo Ablation System, all individual residual risks were controlled and reduced to as far as possible. An acceptable level per the risk acceptability criteria set forth in the risk management plan was achieved.

15.4 Risks Associated with Participation in this Clinical Investigation

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

15.5 Steps Taken to Control or Mitigate Risks

In-depth recommendations and special precautions are included in the IFU.
Risks associated with this clinical investigation are minimized through investigator selection and training, pre-specified patient eligibility requirements, and study monitoring to ensure adherence to the protocol. All adverse events and device deficiencies will be reported to the Sponsor and will be monitored internally for safety surveillance purposes.

15.6 Risk to Benefit Rationale

The cumulative effect of all residual risks have been evaluated to ensure the overall residual risk of the product is acceptable and that the benefits of the device outweigh the overall residual risk.

APPENDIX I: REFERENCES

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APPENDIX II: ABBREVIATIONS AND ACRONYMNS

Acronyms/Abbreviation	Terms
AAD	Antiarrhythmic Drug
ADE	Adverse Device Effect
AE	Adverse Event
AEF	Atrio-esophageal Fistula
AF	Atrial Fibrillation
AFL	Atrial Flutter
ARDS	Acute Respiratory Distress Syndrome
AT	Atrial Tachycardia
AV	Atrioventricular
AVNRT	Atrioventricular Nodal Reentry Tachycardia
BMI	Body Mass Index
CFR	Code of Federal Regulations
CABG	Coronary Artery Bypass Graft
CVA	Cerebrovascular Accident
DOE	Dyspnea on Exertion
DVT	Deep Vein Thrombosis
ECG	Electrocrdiography
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HCT	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
HRS	Heart Rhythm Society
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
IVC	Inferior vena cava
ISO	International Organization for Standardization
ITT	Intent to Treat
LA	Left atrium
LAA	Left Atrial Appendage
LBBB	Left Bundle Branch Block
LOM	Ligament of Marshall
LVEF	Left Ventricular Ejection Fraction
MAE	Major Adverse Event
MDR	Medical Device Reporting
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
OAC	Oral Anticoagulant
PE	Pulmonary Embolism
PI	Principal Investigator
PCW	Pulmonary Capillary Wedge

PRBC	Packed Red Blood Cells
PV	Pulmonary vein
PVI	Pulmonary Vein Isolation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOB	Shortness of Breath
SOC	Standard of Care
SSS	Sick Sinus Syndrome
SVC	Superior vena cava
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram (graphy)
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

APPENDIX III: DEFINITIONS

BLOOD AND LYMPHATIC SYSTEM DISORDERS

Severe anemia: Hematocrit below 25%. Generally, an accepted value to consider the need for transfusion of red blood cells. This is not in the setting of acute persistent bleeding.

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 heart rate of greater than 100 bpm for at least 30 seconds or requiring termination due to hemodynamic compromise.
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 non-conducted 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: See Cardiac Tamponade/Perforation definition.

Cardiac Tamponade/Perforation: Cardiac tamponade/perforation is defined as a complication of AF ablation if the development of a significant pericardial effusion occurs during or within 30 days of undergoing an AF Ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a pericardial effusion of 1 cm or more (by echocardiography). Cardiac tamponade/perforation should be classified as “early” or “late” depending on whether it is diagnosed during or following initial discharge from the hospital.

Cardiogenic Shock: Subject 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 in the context of 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), 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.

Myocardial Perforation: See Cardiac Tamponade/Perforation definition.

Pericardial effusion: Fluid detected in the pericardial space by standard imaging techniques (e.g., echocardiography).

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 embolus, 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. 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.

Hernia: an anatomical part (such as section of the intestine) protrudes through an opening, tear, or weakness in the abdominal wall musculature.

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.

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 failure that requires dialysis:** a significant decrease in renal function requiring dialysis.
- **Renal Insufficiency:** An increase in serum creatinine of ≥1.0 mg/dl over previous value.

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 subject 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 finger nails, 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.
- **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
- **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.

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.

Stroke diagnosis will be performed preferably with positive neuroimaging study. The stroke will be assessed as Minor or Major based on the following:

- Minor—Modified Rankin (mRS) score <2 at 30 and 90 days
- Major—Modified Rankin (mRS) score >2 at 30 and 90 days

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. subject 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: Subject 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 subject’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

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.

Major Bleeding: The following will constitute major bleeding events:

- Fatal bleeding OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR
- Bleeding causing hypovolemic shock or severe hypotension requiring surgery OR
- Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units

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.

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 IV: RATES OF FORSEEABLE ADVERSE EVENTS

Adverse Events that may be anticipated in this clinical study are believed to be consistent with those associated with other invasive surgical and cardiac procedures.

Complications that may have occurred at any time during the procedure, post procedure or that are possible during the follow-up period with the AtriCure cryoICE System 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
- 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
- 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
- Extension of cardiopulmonary bypass
- Extension of extracorporeal bypass
- Esophageal rupture
- Formation of unwanted scar tissue
- Gastro-intestinal bleed
- Gastric motility disorders
- Hematoma
- Hemothorax

- Hemorrhagic stroke secondary to anticoagulant therapy
- Hypertension
- Hypotension
- Infection or fever
- Ischemia
- Major bleeding
- 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 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
- 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)
- Stroke (resulting in neurological deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing infarction)
- 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
- 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.

APPENDIX V: INFORMED CONSENT FORM

A copy of the Sponsor Informed Consent Form Template can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation and will be provided to study sites for IRB/EC approval.

APPENDIX VI: SITE CONTACT INFORMATION

A copy of contact information for each participating site can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

APPENDIX VII: REVISION HISTORY

Amendment Number	Version	Date	Details	Rationale
Not Applicable	A	02Aug2021	Initial Release	NA

FREEZE-AFIB Clinical Study Protocol_Rev A_02AUG2021_Clean

Final Audit Report 2021-08-09

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