Cryterion Cardiac Cryoablation System CE Mark Study

Study ID: CEM-A02-02

ClinicalTrials.gov ID: NCT03723070

This document includes

- **CEM-A02-02 Protocol (PR-004382 Rev 3)**
  - Date: 04 September 2019
  - Page 3-5 includes the revision history of previous versions

Cryterion Cardiac Cryoablation System

CE Mark Study

Protocol: CE Mark Study (CEM-A02-02)

Version: Amendment 03

Date: 04 September 2019

Sponsor:

Cryterion Medical, Inc.
1949 Palomar Oaks Way
Suite 100
Carlsbad, CA 92011
Tel: *+1(760) 206-7910*

Boston Scientific Corporation
4100 Hamline Avenue N
Arden Hills,
MN 55112-5798, USA

Boston Scientific International S.A.
Le Val Saint-Quentin,
2 rue René Caudron,
78960 Voisins le Bretonneux, France

Boston Scientific Pty. Ltd.
Level 5
247 Coward St.
Mascot
NSW
Australia 2020

This study is to be performed in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and the International Conference on Harmonization E6 and ISO standards 14155:2011

permission of Cryterion Medical Persons to whom the information is disclosed must be informed that this and future information is privileged or confidential.

Protocol Signature Page

Protocol: Cryterion Cardiac Cryoablation System

CE Mark Study (CEM-A02-02)

Amendment 03

The signature below constitutes the approval the approval of this Clinical Investigational Plan (CIP) and provides assurances that this clinical study will be conducted in accordance with all stipulation of the CIP including all statements regarding patient confidentiality. The CIP will be followed according to all national and local legal and regulatory requirements.

_____

Site investigator Printed Name

_____ _____

Site investigator Signature Date

Revision History

Revision	DCO	Description of Document Changes
FIM-01	002906	Initial Release
CEM-A01-01 Amendment 01	004383	Study Title change – based on pre-clinical assessment by Notified Body clinical reviewer. Added appropriate references to DIN EN ISO 14155 at the request of the Notified Body clinical reviewer Added acute procedure success, treatment success based on increased follow-ups at 3, 6, and 12 months. Amended protocol to become a multi-center, open label, prospective, open enrollment study to document the long-term effectiveness and safety of the Cryterion Cardiac Cryoablation System. Added early persistent AF patients to inclusion criteria. Addition of 24 Holter monitoring/arrhythmia patch to assist with monitoring potential chronic atrial arrhythmias at 3, 6, and 12 months. Incorporated clinical center's standard of care for post AF ablation follow-up for symptom driven assessments to detect recurrent AF as well as adverse events. Safety data to be compared to historical safety event rate from current market approved AF ablation systems. Added guidance for training and handling of the Cryterion Cardiac Cryoablation System, as well as, venous access and trans-septal approach at the request of the Notified Body clinical reviewer. General Device Description including names, function, device classification, and model numbers now in Appendix A. Appendix B is the ICF. Appendix C is the Case Report Forms.

CEM-A02-02 Amendment 02	004927	Updated Sponsor(s) to include supporting Sponsor(s) associated with Boston Scientific OUS Offices. Primary Effectiveness Endpoint: removed the wait period for confirming PVI. Secondary Endpoint: removed the wait period for confirming PVI. Removed references to the Circular Mapping Catheter (25mm), not supported in the study. Follow Up Schedule: Allowed for any additional visit and any additional procedure (> Day 0). Proposed Indication for Use – inclusive of paroxysmal patient population. Definition of phrenic nerve paralysis clarified. Clarified the definitions of enrolled subjects. Clarified baseline visit assessments. Revised anticoagulation parameters. Revised device return process. Clarified Adverse Event definitions. Clarified device deficiencies. Appendix B: Informed Consent Form (ICF) revised to reflect BSC requirements.

CEM-A02-02 Amendment 03	005791	• Update Revision table: ○ in the 'revision' column, the version (Amendment #) of the previous protocols was added • Update sponsor names in section "Summary of the Cryterion CE Mark study" to align with the page 1 content • Update Table 1 to add POLARx CM-CATH-03 and CM-CATH-04 device • Update of Table 2 to align with text in section 3.3.1 • Update of section 2.4.1.1 Study Endpoint to align with the endpoints as described in section "Summary of the Cryterion CE Mark study" • Update of the term 'Cryterion Medical' throughout the document to 'the sponsor' • Update wording of definitions of a serious adverse event in section 5 • Update death notification timelines in Table 3 and section 5.3 to be consistent. • Addition of device experience reporting timelines in section 5.4 to match Table 3

Table of Contents

SUMMARY OF CRYTERION CE MARK STUDY

Study Title	Cryterion Cardiac Cryoablation CE Mark Study Amendment			
Device Name	The Cryterion Cardiac Cryoablation System			
Study Device Components	The Cryterion Cardiac Cryoablation System consists of: The Cryterion Cryoablation Balloon Catheter (PolarX) The Cryterion Circular Mapping Catheter (PolarMap) The Cryterion Steerable Sheath (PolarSheath) The Cryterion SmartFreeze Cryoablation Console Cryterion Accessories (connection cables, mechanical & electrical) Cryterion Optional Accessories (foot pedal switch, tablet interface) ***{Model Numbers are in Table 1 below}***			
Indication for Use (Proposed)	The Cryterion Cardiac Cryoablation System is intended for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of atrial fibrillation.			
Sponsors	Cryterion Medical, Inc. 1949 Palomar Oaks Way Suite 100 Carlsbad, CA. 92011 USA	Boston Scientific Corporation 4100 Hamline Avenue N Arden Hills, MN 55112-5798, USA	Boston Scientific International S.A. Le Val Saint-Quentin, 2 rue René Caudron, 78960 Voisins le Bretonneux, France	Boston Scientific Pty. Ltd. Level 5 247 Coward St. Mascot NSW Australia 2020
Study Objective	The clinical study objective is to demonstrate the acute and 12 months safety and performance of the Cryterion Cardiac Cryoablation System when used as intended.			
Study Design	Multi-center, open label, prospective, open enrollment study to document the safety and performance of the Cryterion Cardiac Cryoablation System.			

Primary Effectiveness Endpoint	**Acute Procedural Success (APS)** Acute procedural success is defined as the documentation of pulmonary vein isolation for each of the targeted veins at the end of the first protocol-defined (index) cryoablation procedure. Documentation will be completed with the Cryterion Circular Mapping Catheter to confirm PVI. The physician should confirm and document entrance and exit block by standard of care pacing maneuvers during the index procedure.
Additional Effectiveness Endpoint	**Treatment Success** Treatment success at 12 months will be determined by evaluating the proportion of subjects free from symptomatic atrial arrhythmias. A treatment failure is defined as a subject being an acute procedural failure, having more than one repeat procedure during the 90-day blanking period or having a documented, symptomatic episode(s) of atrial fibrillation or atrial tachycardia, between 91 and 365 days post index procedure. Occurrence or recurrence of a right atrial arrhythmia is not considered a treatment failure post the 90-day blanking period. Assessments will be made via 12-lead electrocardiogram measurements at 3, 6 and 12-month visits (including unscheduled visits for symptomatic atrial arrhythmias). In addition, a 24-hour Holter (wearable arrhythmia monitor/ patch) will be assessed at the 3, 6 and 12-month visits (including unscheduled visits for symptomatic atrial arrhythmias).
Primary safety endpoint	Safety endpoint is assessed by freedom from device or procedure related serious adverse events (referred to as Major Adverse Events, MAE) occurring up to 12 months post index procedure. MAEs include the following: • Death • Myocardial infarction • Cardiac perforation/ pericardial tamponade • Cerebral infarct or systemic embolism • Major bleeding requiring transfusion of blood products • Mitral or tricuspid valvular damage • Phrenic nerve palsy causing persistent diaphragmatic paralysis • Symptomatic pulmonary vein stenosis • Atrio-esophageal fistula • Air embolism leading to a life-threatening event such as a ventricular arrhythmia, stroke or myocardial infarction • Any other serious or non-serious adverse device effects (SADEs or ADEs)

Sample Size	Up to 100 treated subjects
Study locations	Up to 10 clinical sites in the EU and NZ
Study Duration	Enrollment is expected to take 7 - 9 months. Follow-up will occur at discharge, and 1, 3, 6 and 12 months.
Secondary Endpoints	Secondary endpoints include: • All Procedure and device related adverse events • Documentation of all PVs that demonstrate isolation immediately post ablation and then show reconnection during entrance/exit block testing • Operator's assessment of handling characteristics (through a System Performance Questionnaire) compared to commercially available sheaths circular mapping catheters and balloon ablation technologies
Inclusion Criteria Subjects must:	• Male or female between the ages of 18 and 80 years • Currently scheduled for a de novo ablation of paroxysmal atrial (PAF) defined as AF with self-terminating episodes lasting no longer than 7 continuous days. • Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full duration of the clinical study. • Willing and able to give informed consent

Exclusion Criteria Subjects must not:	Exclusion Criteria EC 1 In the opinion of the Investigator, any known contraindication to an AF ablation, TEE, or anticoagulation EC 2 Any duration of continuous AF lasting longer than 7 days EC 3 History of previous left atrial ablation or surgical treatment for AF/AFL/AT EC 4 Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause EC 5 More than four (4) electrical cardioversions in the year prior to enrollment excluding cardioversions performed within 24 hours of arrhythmia onset. EC 6 Structural heart disease or implanted devices as described below: a. Left ventricular ejection fraction (LVEF) < 40% based on the most recent TTE (≤ 6 months) b. Left atrial diameter > 50 mm or a left atrial volume index >50 ml/m^2 based on the most recent TTE (≤ 6 months, one measurement of the two being sufficient) c. An implanted pacemaker or ICD d. Previous cardiac surgery: ventriculotomy, or atriotomy (excluding atriotomy for CABG) e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve f. Interatrial baffle, closure device, patch, or PFO occluder g. Presence of a left atrial appendage occlusion device h. Presence of any pulmonary vein stents i. Coronary artery bypass graft (CABG) or PTCA procedure within the last 90 days. j. Unstable angina or ongoing myocardial ischemia k. Previous myocardial infarction (≤ 6 months) l. Moderate or severe mitral insufficiency noted on the most recent TTE (≤ 6 months) EC 7 Any previous history of cryoglobulinemia EC 8 History of blood clotting or bleeding disease EC 9 ANY prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative DVT) EC 10 Pregnant or lactating (current or anticipated during study follow up) EC 11 Current enrollment in any other study protocol where testing or results from that study may interfere with the procedure or outcome measurements for this study EC 12 Any other condition that, in the judgment of the

	investigator, makes the subject a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable subject population, mental illness, addictive disease, terminal illness with a life expectancy of less than two years, extensive travel away from the research center) <u>Secondary Screening: subject or conducted per physician discretion according to institution's SOC</u> EC 13 Any pulmonary vein diameter >30 mm as evidenced by CT scan, LA venogram or intracardiac echo (ICE) EC 14 A common left pulmonary vein ostium as evidenced by CT scan, LA venogram or intracardiac echo that in the judgment of the investigator makes the subject a poor candidate for this study
Data Collection at Follow-up	***See Table 2 below for follow-up schedule***

Table 1: Cryterion Cardiac Cryoablation System Components and Accessories Model Numbers

Component	Device Class	Model Number
Cryoablation Balloon Catheter	III	CM-CATH-01 (Short tip, 5mm), 28mm diameter
		CM-CATH-02 (Long tip, 12mm), 28 mm diameter
		CM-CATH-03 (Short tip), 28mm diameter
		CM-CATH-04 (Long tip), 28mm diameter
Cryo-Console	IIa	CM-CONS-01
Circular Mapping Catheter	III	CM-CATH-10 (20mm)
Steerable Sheath, 12 F	III	CM-CATH-20
Diaphragm Movement Sensor	IIa	CM-ACCS-07
Inter Connection Box	I	CM-ACCS-05
Cryo-Console Foot Switch	I	CM-ACCS-06
Cryo-Cable	I	CM-ACCS-01
Cryo-Catheter Extension Cable	I	CM-ACCS-02
EP Electrical Cable	I	CM-ACCS-03

Table 2: Follow-Up Schedule

	Screening & Baseline	Index Procedure Day 0[2]	Discharge (0 to 7 days)	1 month (30 ± 7 days)	3 months (90 +/- 14 days)	6 months (180 +/- 30 days)	12 months (360 +/- 30 days)	Additional visit	Additional Procedure (> Day 0)
CIP Informed Consent	X								
Eligibility Review	X								
Medical History	X			X					
Physical Exam	X		X	X	X	X	X	(X) optional	
Medications	X	X	X	X	X	X	X	(X) optional	X
Transthoracic Echocardiogram (TTE)	X								
CT scan, Trans Esophageal Echo (TEE) or intracardiac echo (ICE) to R/O LA Thrombus		X (CT/TEE within 72 hours of procedure)							(X) Following Procedural Standard of care
CT scan, ICE or Pulmonary Venogram to r/o common ostium or enlarged PV diameter[1]	(CT scan)	ICE or (Pulmonary Venogram)							
Device data		X							X
Adverse Events	X	X	X	X	X	X	X	(X) optional	X
12-lead ECG	X	X	X	X	X	X	X	(X) optional	X
24 Hour Holter/Arrhythmia Patch					X	X	X	(X) optional	
Labs (per SOC)	X								
HCG (female subjects of child bearing potential)	X								

[1]Only one of these tests is required to establish common PV ostium and/or enlarged PV diameters

[2]All subsequent visits are counted in days from the index procedure

1 INTRODUCTION

1.1 Background

Supraventricular tachycardias (SVTs) are a collective group of arrhythmias that originate superior to the ventricles and most notably in the upper chambers (atria) of the heart. SVTs can cause the heart to beat very rapidly or erratically with rates more than 100 beats per minute (bpm). The arrhythmia is generally well tolerated but may produce clinical symptoms such as light-headedness, chest palpitations, shortness of breath, fatigue, and/ or exercise intolerance. In more serious SVTs, the heart may beat less efficiently, leading to potentially inadequate blood supply to vital organs and formation of thrombus in the heart, thus increasing the risk of systemic embolic events, including stroke.

The most common forms of SVTs include atrial fibrillation (AF), and a variety of non-AF rhythms, including atrial flutter (AFL), atrial tachycardia (AT), and atrioventricular (AV) nodal reentrant tachycardia (AVNRT).

Atrial Fibrillation

Atrial fibrillation (AF) is among the most prevalent arrhythmias in the world today affecting approximately 33.5 million subjects worldwide.[1] The age of subjects with AF is steadily rising and now averages between 75 and 85 years of age. AF is associated with a five-fold risk of stroke, a three-fold incidence of congestive heart failure, and higher mortality.[2]

Symptoms arise from the rapid, irregular rhythm as well as cardiac hemodynamic changes related to uncoordinated atrial contractions. These uncoordinated contractions also allow blood to pool in the atria and may ultimately lead to thromboembolism and stroke.

AF is characterized by a chaotic contraction of the atrium in which an electrocardiogram (ECG) recording is necessary to diagnose the arrhythmia. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long

[1] Chugh S, Havmoeller R, Narayanan K, et al. Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. CIRC. 2014;129(8):837-847.

[2] Camm AJ, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*, 2012 Oct; 14(10):1385-413

enough for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm strip, should be considered an AF episode.[3,4]

The diagnosis requires an ECG or rhythm strip demonstrating: (1) irregular RR intervals (in the absence of complete AV block), (2) no distinct P waves on the surface ECG, and (3) an atrial cycle length (when visible) that is usually variable and less than 200 milliseconds.[3]

AF can be characterized into four classifications:

1. Paroxysmal AF (PAF) is defined as recurrent AF (≥ two episodes) that terminates spontaneously or with intervention within seven days of onset.[3]
2. Early Persistent AF is defined as AF that is sustained for seven days but is less than 3 months in duration.[3]
3. Persistent AF is defined as continuous AF that is sustained beyond seven days. Long-standing persistent AF is defined as continuous AF of greater than one year's duration.[3]
4. Permanent AF is defined as AF in which the presence of the AF is accepted by the subject (and physician). Within the context of any rhythm control strategy, including catheter ablation, the term permanent AF is not meaningful. The term permanent AF represents a joint decision by the subject and a physician to cease further attempts to restore and/ or maintain sinus rhythm at a point in time.[3]

For many years, three major schools of thought competed to explain the mechanism(s) of AF: multiple random propagating wavelets, focal electrical

[3] Calkins H, Hindricks, G, Cappato, R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. Vol. 10, October 2017

[4] Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* Oct 2010;31(19):2369–2429

discharges, and localized reentrant activity with fibrillatory conduction.[5,6,7,8,9] Significant progress has been made in defining the mechanisms of initiation and perpetuation of AF. One of the most important breakthroughs was the recognition that, in a subset of subjects, AF was triggered by a rapidly firing focus and could be "cured" with a localized catheter ablation procedure.[10,11] This landmark observation caused the electrophysiology (EP) community to refocus its attention on the pulmonary veins (PVs) and the posterior wall of the left atrium (LA), as well as the autonomic innervation in that region. It also reinforced the concept that the development of AF requires a "trigger" and an anatomic or functional substrate capable of both initiation and perpetuation of AF.

Sustained high rates in the atrium and/ or the presence of heart disease are associated with structural and electrophysiological remodeling of the atria and can alter the substrate even further, helping to perpetuate AF.[12] Atrial fibrillation can also be the result of preexisting atrial disease. Although much has been learned about the mechanisms of AF, they are not completely understood. Because of this, in the great majority of AF subjects, it is not yet possible to precisely tailor an ablation strategy to an AF mechanism.

3D Electroanatomic Mapping

In the interventional treatment of arrhythmias (ablation), the electrical circuits or pathways may be "mapped" by moving heart catheters to various locations

[5] Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res*. May 2002;54(2):204–216.

[6] Nattel S. New ideas about atrial fibrillation 50 years on. *Nature*. Jan 10 2002; 415(6868):219–226.

[7] Dobrev D, Voigt N,Wehrens XH. The ryanodine receptor channel as a molecular motif in atrial fibrillation: pathophysiological and therapeutic implications. *Cardiovasc Res*. Mar 1 2011;89(4):734–743.

[8] Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev*. Jan 2011;91(1):265–325.

[9] Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J Clinical Invest*. Aug 1 2011;121(8):2955–2968

[10] Jais P, Haissaguerre M, Shah DC et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation*. Feb 4 1997;95(3):572–576.

[11] Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. Sep 3 1998; 339(10):659–666.

[12] Everett TH 4th, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. Am J Physiol Heart Circ Physiol. Dec 2006;291(6):H2911–2923

within the presumed pathway and measuring the timing of the conduction. In the past twenty years, more intricate mapping systems have been developed to provide electrical as well as geometrical representation of the chambers of the heart. Referred to as three dimensional (3D) electroanatomic mapping systems, the development of these systems has progressed rapidly and now include both contact and noncontact mapping systems. During an ablation procedure, these devices can provide better diagnostic value and guide ablation strategies.[13] Additionally, electromagnetic navigation systems have been shown to substantially reduce the fluoroscopy time required for AF ablation.[14,15,16] In a recent worldwide survey of AF ablation methods, nearly 50% of procedures included the navigation means.[17]

RF Ablation Catheters

Radiofrequency (RF) ablation remains the energy source of choice for ablation. In the worldwide survey of AF ablation methods, 98% of ablations were completed with RF energy while < 2% completed a thermal injury to the endocardium with cryoablation.[17] This included both irrigated and non-irrigated RF ablation catheters.

Force Sensing RF Ablation Catheters

To improve on ablation lesion characteristics and durability, two new catheters have recently been developed. Described as "contact-force sensing" catheters, these new designs remove much of the operator dependence on the force applied to the endocardial surface during an ablation. Recent publications have

[13] Hindricks G, Willems S, Kautzner J, De Chillou C, Wiedemann M, Schepel S, Piorkowski C, Risius T, Kottkamp H; EuroFlutter Investigators. Effect of electroanatomically guided versus conventional catheter ablation of typical atrial flutter on the fluoroscopy time and resource use: a prospective randomized. J Cardiovasc Electrophysiol. 2009 Jul;20(7):734-40.

[14] Sporton SC, Earley MJ, Nathan AW, Schilling RJ. Electroanatomic versus fluoroscopic mapping for catheter ablation procedures: a prospective randomized study. J Cardiovasc Electrophysiol. 2004 Mar;15(3):310-5.

[15] Kottkamp H, Hügl B, Krauss B, Wetzel U, Fleck A, Schuler G, Hindricks G. Electromagnetic versus fluoroscopic mapping of the inferior isthmus for ablation of typical atrial flutter: A prospective randomized study. Circulation. 2000 Oct 24;102(17):2082-6.

[16] Smeets JL, Ben-Haim SA, Rodriguez LM, Timmermans C, Wellens HJ. New method for nonfluoroscopic endocardial mapping in humans: accuracy assessment and first clinical results. Circulation. 1998 Jun 23;97(24):2426-32.

[17] Cappato R, Calkins H, Chen SA, et al. Updated Worldwide Survey on the Methods, Efficacy, and Safety of Catheter Ablation for Human Atrial Fibrillation. Circ Arrhythmia Electrophysiology. 2010;3:32-38.

demonstrated improvement in PV isolation and longer-term outcomes for ablation when the percentage of time the ablation catheter is in stable contact is increased.[18,19,20,21]

Cryoablation

Cryoablation has gained significant popularity and utilization worldwide. With the understanding the pulmonary veins may be the "cornerstone" of ablation strategies, a cryo balloon has been developed to provide a "single shot" therapy for isolation of the pulmonary veins. By navigating the balloon to the ostium of the PV and occluding flow, a PV may be isolated with a single cryoablation of 3 - 4 minutes. The currently approved technology (Artic Front™/ Arctic Front Advance™ Cryoablation Balloon, Medtronic®) has completed two landmark studies demonstrating efficacy for PAF management of approximately 70% and 65% respectively.[22,23]

Complications arising from cryoablation are consistent with those of heat-based therapies. Additionally, as the balloon is placed in the right-sided PVs and near the phrenic nerve, diaphragm paralysis, (both transient and permanent), has been reported. To mitigate this risk, pacing maneuvers and continuous analysis of diaphragmatic movement has been used.

[18] Sohn C, Williams S, Chubb H, et al. Catheter Contact Force: A Review of Emerging Techniques and Technologies in AF Ablation.

[19] Natale A, Reddy V, Monir G, et al. Paroxysmal AF Ablation with a Contact Force Sensing Catheter. Journal American College of Cardiology 2014;64:647-56.

[20] Reddy V, Dukkipati S, Neuzil P, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation. Circulation. 2015;132:907-915.

[21] Barnett A, Bahnson T, Piccini J. Recent Advances in Lesion Formation for Catheter Ablation of Atrial Fibrillation. Circ Arrhythmia Electrophysiology, June 2016;9 e003299.

[22] Packer D, Kowal R, Wheelan K, Irwin J, et al. Cryoballoon Ablation of Pulmonary Veins for paroxysmal Atrial Fibrillation. JACC.2013;61:1713-23.

[23] Kuck KH, Brugada J, Fu¨ rnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albeneque JP, Tondo C, for the FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374:2235–2245.

2 THE CRYTERION CARDIAC CRYOABLATION SYSTEM (SYSTEM).

2.1 General Device Description

The Cryterion Cardiac Cryoablation System is designed to thermally ablate cardiac tissue in the management of atrial fibrillation. The components and accessories for the system are listed in Table 1. A detailed device description is provided in Appendix A.

2.2 Proposed Indication for Use Statement

The Cryterion Cardiac Cryoablation System is indicated for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of Paroxysmal Atrial Fibrillation (PAF).

2.3 Clinical Study Objective

The clinical study objective is to demonstrate the acute and 12 months safety and performance of the Cryterion Cardiac Cryoablation System when used as intended.

2.4 Clinical Study Design

The study is a non-randomized, open label, prospective multi-center, clinical study designed to collect long-term (1 year), system-related, clinical and subject reported outcome data from subjects indicated for a de novo ablation of paroxysmal atrial fibrillation and treated with the Cryterion Cardiac Cryoablation System and components including the SmartFreeze Cryo-console, the Cryoablation Balloon Catheter, and the Circular Mapping catheter.

This protocol is an amendment of the original version initiated in May 2018 designed for the purpose of obtaining CE mark and is intended to prolong the follow-up period to 12 months and extend the number of enrolled subjects from 30 to 100.

Subjects will be followed for 12 months by each clinical center with specific scheduled visits to detect recurrent AF (Detectable AF) and adverse events (AEs).

The diagram in Figure 1 is a simplified schematic of the study structure for evaluating the primary outcomes for subjects enrolled in the study, as formally described in other sections of this protocol.

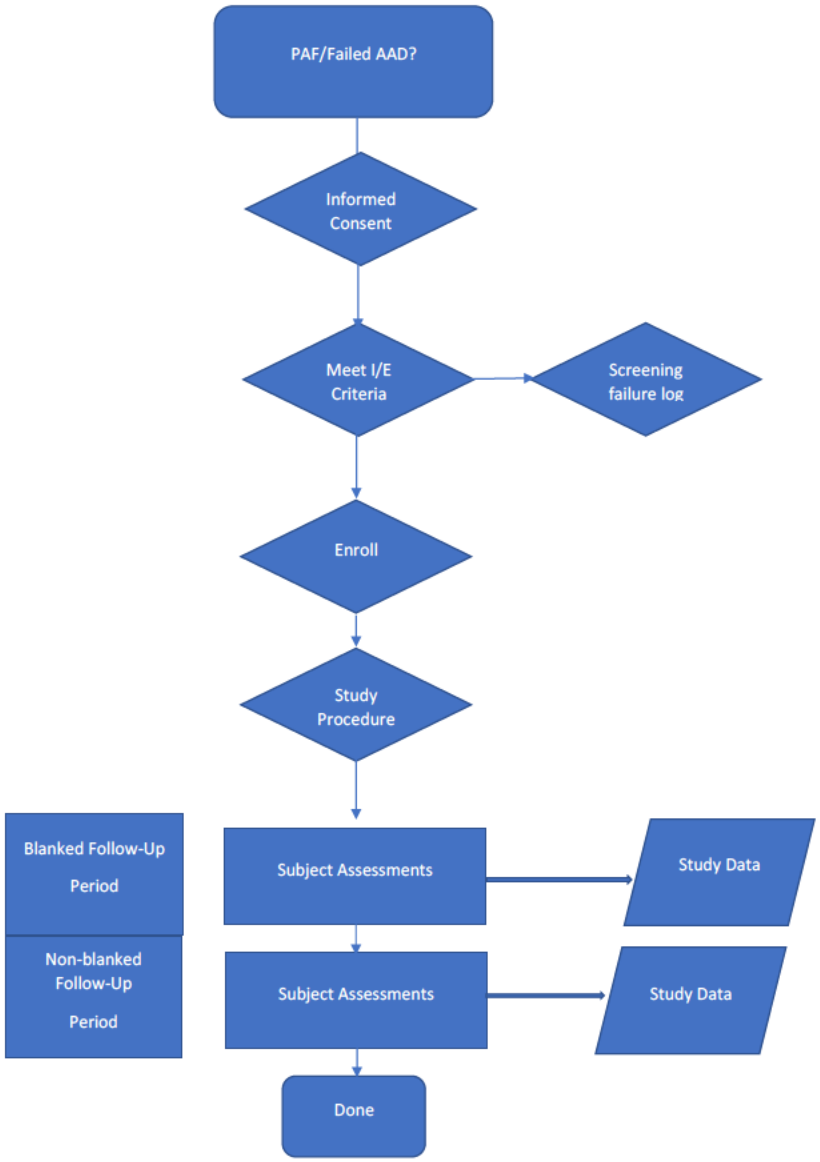

Figure 1. study diagram

2.4.1 Study Endpoints

2.4.1.1 Primary safety endpoint

Safety endpoint is assessed by freedom from device or procedure related serious adverse events (referred to as Major Adverse Events, MAE) at 12 months post-procedure.
MAEs include the following:

- Death
- Myocardial infarction
- Cardiac perforation/ pericardial tamponade
- Cerebral infarct or systemic embolism
- Major bleeding requiring transfusion of blood products
- Mitral or tricuspid valvular damage
- Phrenic nerve damage causing persistent diaphragmatic paralysis*
- Symptomatic pulmonary vein stenosis
- Atrio-esophageal fistula
- Air embolism leading to a life-threatening event such as a ventricular arrhythmia, stroke or myocardial infarction
- Any other serious or non-serious adverse device effects (SADEs or ADEs)

*Note: according to the consensus document definition3: Phrenic nerve paralysis is defined as absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis in this study is considered to be permanent when it is documented to be present at 12 months following ablation.

2.4.1.2 Primary effectiveness endpoint: acute procedural success.

The Primary Effectiveness Endpoint is the rate of successful pulmonary vein electrical isolation with confirmation of entrance and exit block achieved with the Cardiac Cryoablation System (Acute procedural success).
Acute procedural success is defined as the documentation of pulmonary vein isolation following the last cryo application for each of the targeted veins. Demonstration of electrical isolation in ≥ 3 PVs or their anomalous equivalents at the end of the first protocol-defined cryoablation procedure Documentation will be completed with the Cryterion Circular Mapping Catheter to confirm PVI. The physician should confirm and document entrance and exit block by standard of-care pacing maneuvers during the index procedure.

2.4.1.3 Additional effectiveness endpoint: 12 months treatment success

Treatment success is defined as the proportion of subjects free from symptomatic atrial arrhythmias at 12 months. A treatment failure is defined as a subject being an acute procedural failure, having more than one repeat procedure during the 90-day blanking period or having a documented, symptomatic episode(s) of atrial fibrillation or atrial tachycardia, between 91 and 365 days post index procedure (windows allowed per protocol as shown in Table 2 included). Occurrence or recurrence of a right atrial arrhythmia is not considered a treatment failure post the 90-day blanking period.

2.4.1.4 Secondary endpoints

Secondary Endpoint Measurements will include:

- All Procedure and device related adverse events*
- Documentation of all targeted PVs that demonstrate isolation immediately post ablation and then show reconnection during entrance/exit block testing
- Recording of time to demonstration of PVI using the Circular Mapping catheter following the initiation of a freeze cycle
- Operator's assessment of handling characteristics with a System Performance Questionnaire**

* be accessed directly from the clinical database (eCRFs hosted on IBM Clinical platform)

** The System Performance Questionnaire is included in the study clinical database and includes questions to the operator to assess quality characteristics of the products, alone and compared to commercially available cryoballoon ablation technologies and circular mapping catheters. The system performance questionnaire will be used with all new clinical users for the first five (5) cases performed with the Cryterion System. After the first 5 cases, users can use the questionnaire to provide specific product feedback related to user experience(s) on an as needed basis (for example: the ability of the cryoablation system to deal with tortuous anatomy of the LA/PVs). In case the investigator reports

quality issues in the questionnaire, he should consider if needed, to enter a device deficiency (See section 5.4)

2.5 Clinical Study Design Justification

PAF is a recurring arrhythmia that predisposes subjects to embolic phenomena such as stroke. Available treatments include medication, various RF ablation procedures in the atria and PVs, atrioventricular (AV) nodal ablation with pacemaker implantation, and open-heart ablation and surgery (e.g. maze procedure). All these treatments have significant failure rates as well as the potential for significant morbidity.

Cryoablation offers potential advantages. It may have a lower risk of creating endocardial thrombus, PV stenosis and permanent nerve damage than heat-based ablation. Tissue cooling during cryoablation can be rapidly reversed, allowing minimization of unwanted damage while monitoring for adverse effects to conduction tissue and adjacent nerves.

The study is designed as a non-randomized, multicenter study to further evaluate the System in the cryoablation of paroxysmal atrial fibrillation. The subject population has been chosen based on the ability to assess both the cryoablation balloon and the mapping catheter in typical left atrial anatomy. This study was originally designed as a protocol for acute safety and effectiveness evaluation in 30 subjects with a follow up of one month, to support submission for obtaining CE mark. In agreement with the Notifying Body, in order to generate evidence of chronic safety and effectiveness the protocol was amended to increase the sample size to 100 subjects and extend the follow up to 12 months.

De novo subjects are selected as most representative of the population where a cryoballoon may first be used for PVI. To determine the performance of the Cryoablation Balloon Catheter, an analysis of the ability to electrically isolate a targeted PV acutely will be completed. PVI measurements will be taken post cryo application to assess entrance and exit block.

Chronic effectiveness data will be analyzed through 12 months to determine the long-term performance of the System. In addition, adverse events will be collected through the follow-up period. Adverse events rates collected in the study maybe

compared to rates from current market approved AF ablation systems and available from literature.

The Cryterion Cardiac Cryoablation System is a new alternative to the existing Medtronic® Cryoablation Balloon Arctic Front Advance™ technology for the ablation treatment of atrial fibrillation. Descriptive statistics will be utilized to analyze all long-term safety and performance data from this study.

The potential benefits of this study are that cryoablation will reduce or eliminate targeted arrhythmias while minimizing adverse events such as thromboembolism, cardiac perforation, PV stenosis or phrenic nerve damage.

The study protocol and procedures have been designed to minimize risks for study subjects, including the selection and training of qualified Investigators and investigational sites and careful clinical monitoring of study subjects.

2.6 Clinical Study Scale and Duration

The present study plans to enroll up to 100 subjects. Enrollment of the first 30 subjects (for the CE study) has concluded in October 2018. Enrollment of the additional 70 subjects is expected to take an additional 7-9 months. Follow-up for all 100 subjects will occur at discharge and 1, 3, 6 and 12 months resulting in an approximate total study duration of 23-30 months.

2.7 Clinical Study Population

The subject population will consist of men and women between the ages of 18 - 80 years of age scheduled for a de novo percutaneous procedure to ablate atrial fibrillation (AF).

A potential study subject will meet all the following inclusion criteria and none of the exclusion criteria.

2.7.1 Inclusion Criteria

IC 1 Male or female between the ages of 18 - 80 years old.

IC 2 Currently scheduled for a de novo ablation of atrial fibrillation (AF) defined as AF with self-terminating episodes lasting no longer than 7 continuous days (PAF).

IC 3 Willingness, ability, and commitment to participate in baseline and follow-up evaluations for the full duration of the clinical study.

IC 4 Willing and able to give informed consent.

2.7.2 Exclusion Criteria

EC 1 In the opinion of the Investigator, any known contraindication to an AF ablation, TEE, or anticoagulation

EC 2 Any duration of continuous AF lasting longer than 7 days

EC 3 History of previous left atrial ablation or surgical treatment for AF/AFL/AT

EC 4 Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause

EC 5 More than four (4) electrical cardioversions in the year prior to enrollment excluding cardioversions performed within 24 hours of arrhythmia onset.

EC 6 Structural heart disease or implanted devices as described below:

a. Left ventricular ejection fraction (LVEF) < 40% based on TTE based on most recent TTE (≤ 6 months)
b. Left atrial size > 50mm or left atrial volume index >50 ml/m^2 based on most recent TTE (≤ 6 months, one measurement of the two being sufficient)
c. An implanted pacemaker or ICD
d. Previous cardiac surgery: ventriculotomy, or atriotomy (excluding atriotomy for CABG)
e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve
f. Interatrial baffle, closure device, patch, or PFO occluder
g. Presence of a left atrial appendage occlusion device
h. Presence of any pulmonary vein stents
i. Coronary artery bypass graft (CABG) or PTCA procedure within the last 30 days
j. Unstable angina or ongoing myocardial ischemia
k. Previous myocardial infarction (≤ 6 months)
l. Moderate or severe mitral insufficiency noted on baseline TTE (≤ 6 months)

EC 7 Any previous history of cryoglobulinemia

EC 8 History of blood clotting or bleeding disease

EC 9 ANY prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative DVT)

EC 10 Pregnant or lactating (current or anticipated during study follow up)

EC 11 Current enrollment in any other study protocol where testing or results from that study may interfere with the procedure or outcome measurements for this study

EC 12 Any other condition that, in the judgment of the investigator, makes the subject a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable subject population, mental illness, addictive disease, terminal illness with a life expectancy of less than two years, extensive travel away from the research center)

Secondary Screening: subject or conducted per physician discretion according to institution's SOC

EC 1 Any pulmonary vein diameter >30 mm as evidenced by CT scan, LA venogram or intracardiac echo (ICE)

EC 2 A common long left pulmonary vein ostium as evidenced by CT scan, LA venogram or ICE that in the judgment of the investigator makes the subject a poor candidate for this study

2.8 Clinical Study Enrollment Definitions

For the purposes of this clinical study, the following definitions regarding the status of a subject will apply:

Enrolled Subject - Any subject who has signed an informed consent form (ICF)

Consent Ineligible Subject – Any subject who has signed the informed consent but is found not to meet all the inclusion/exclusion criteria. This includes a subject who has signed an informed consent form but may be excluded based on the results of the pre-procedure TEE or intracardiac echocardiogram (ICE) evaluation of the left atrial appendage (LAA) and/or PV anatomy. In the event these Subjects completed a trans-septal puncture, they will be followed through discharge for

the recording of any procedure related adverse events. These patients will not count towards the enrollment ceiling and will not be considered for the primary endpoints analysis.

Intent Subject – Any subject who has signed an informed consent form (ICF) and is deemed study eligible by meeting all the inclusion and none of the exclusion criteria but does not undergo the ablation procedure. This patient will be withdrawn from the study. Data will be collected up to the point of withdrawal, will not count towards the enrollment ceiling and will not be considered for primary endpoints analysis.

Attempt Subject - Any subject who has signed an informed consent form (ICF) and is deemed study eligible by meeting all the inclusion and none of the exclusion/criteria and undergoes the ablation procedure with any of the investigational device entered in the patients' body but no energy is delivered to the PVs. This patient will be followed through the 30 days follow up then withdrawn from the study. Data will be collected up to the point of withdrawal, will not count towards the enrollment ceiling and will not be considered for primary endpoints analysis.

Treated Subject – Any screened subject who completes the ablation procedure to the point that any of the investigational products are introduced into the body and Cryo-energy is delivered. Enrolled subjects will be followed for all study outcome measures for the full duration of the clinical study.

2.9 Subject Withdrawal

Individual subjects may withdraw their consent to participate in the study at any time. Also, an Investigator may discontinue a subject's participation in the study at any time to protect the safety, rights, or welfare of the subjects.

Subjects missing follow-up visits will not be considered lost to follow-up until adequate attempts to contact the subject have been made by telephone, e-mail, and/ or certified/ registered letter. "Adequate attempts" is defined as at least three documented communication attempts (phone or email) with at least two attempts by phone.

If a subject withdraws from the clinical investigation, the reason(s) shall be reported. All open reportable Adverse Events should be closed or documented as chronic. If withdrawal is due to problems related to investigational device safety

or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

All subject withdrawals must be documented on the CRF Exit form and in subject's medical record including the reason for study withdrawal. No more data will be captured after point of withdrawal.

3 CLINICAL STUDY TREATMENTS AND FOLLOW-UP VISITS

3.1 Informed Consent

Informed consent shall be obtained in writing from the subject following the process described in ISO 14155:2011. It is the responsibility of the Investigator to give each subject full and adequate verbal and written information regarding all aspects of the study procedure, device, and associated risks. A signed, informed consent form (ICF) must be obtained from the subject before any study-related procedures or data collection. The subject must sign and date the informed consent form prior to enrollment. Failure to provide informed consent renders the subject ineligible for the study. This form or a modification of it must have prior approval of the study site's Investigational Review Board or Ethics Committee prior to obtaining subject consent. The ICF must be signed by the subjects (or they legally authorized representative). The Investigator (or designee) must also sign the ICF as evidence the proper information regarding the study was provided. The original signed ICF is filed in the subject's study records with one copy placed in the subject's medical notes and one copy provided to the subject.

3.2 Subject Enrollment and Baseline

For enrolled subjects, demographic data and medical history data will be collected, including:

- History of AF and other arrhythmias, including date of first AF diagnosis and number of cardioversions in the last 12 months.
- Medication history including AADs and anticoagulation
- available 12 Lead EGC
- DC Electro-cardioversion (DCCV) history
- Information supportive of determining a $CHADS_2$ score

- Most recent (≤ 6 months) transthoracic echocardiogram (TTE) will be reviewed to document:
  - Left atrial size or volume
  - Left ventricular ejection fraction
  - Severity of any valvular heart disease

The subject will undergo a baseline visit that will include Physical assessment and ECG.

CT Scan, TEE, ICE or pulmonary venogram will be used to assess pulmonary vein anatomy and diameters and evidence of left-atrial thrombus according to table 2 Follow up schedule.

Additional testing:

- Pregnancy test (if applicable)
- Routine standard of care laboratory and x-ray tests for pre-ablation work-up

3.3 Ablation Procedure

3.3.1 Determination of Left Atrial Thrombus

Determination of any left atrial or left atrial appendage thrombus requires the use of either a TEE/CT scan performed within seventy-two (72) hours prior to the ablation procedure or an ICE performed during the procedure once vascular access is obtained. Proper placement of the ICE catheter for LAA visualization should follow the Investigator's standard of care. If any evidence of atrial thrombus is discovered, the procedure will not be performed at that time. The subject will be considered a screen failure and exited from the study.

3.3.2 Anticoagulation

Use of anticoagulation leading up to the procedure should be dictated by standard of care for the institution. During the ablation procedure, an Activated Clotted Time (ACT) > 300 seconds should be achieved before the trans septal puncture is performed and immediately followed by an intravenous (IV) heparin bolus with repeat heparin administration, administered as necessary, to achieve an ACT greater than 350 seconds prior to ablation. Once a therapeutic ACT has been achieved, the activated clotting time (ACT) shall be monitored and recorded every thirty (30) minutes throughout the procedure to maintain the required

level. If the ACT value decreases below 350 seconds, additional heparin should be given, and the procedure may continue at the discretion of the investigator.

Upon removal of the catheters and the trans septal sheath from the left atrium, IV heparin may be discontinued. The vascular access sheaths will be removed when the ACT reaches a clinically acceptable level. The use of protamine to reverse heparin effects is at the discretion of the Investigator. Continuation of all oral anticoagulation should follow the standard-of-care for the institution. Anticoagulation medications shall be documented on the Concomitant Medication eCRFs.

3.3.3 Antiarrhythmic Medications (AADs)

The use of oral antiarrhythmic medications (AADs) leading up to an ablation procedure is at the discretion of the Investigator.

3.3.4 Venous Access and Trans Septal Puncture

The placement of venous introducer sheaths should follow the institution's standard-of-care for an AF ablation procedure.

A single or double trans-septal (TS) puncture is performed. One left atrial sheath compatible with the Cryoablation Balloon is required. Methods to perform the TS puncture shall follow the institution's standard-of-care. It is recommended the initial sheath placement into the left atrium is appropriately sized to accommodate the mapping catheter. Sizing up to the Cryterion sheath should occur following the initial PV mapping.

Since the protocol requires a large bore sheath and catheter exchanges in the left atrium, there is an increased risk of air emboli. Left atrial sheath management of flushing and fluid infusion shall meticulously follow the lab's standard-of-care and applicable Instructions for use (IFU).

3.3.5 Pulmonary Vein Mapping with the PolarMap Circular Mapping Catheter

Prior to the introduction of the Cryterion PolarX Cryoablation Balloon Catheter, baseline mapping of the pulmonary veins must occur using the PolarMap Mapping Catheter. Each targeted vein must have a recording. Tracings generated by the EP recording system are required as a procedure source document.

3.3.6 Steerable Sheath Preparation and Placement

Preparation and deployment of the Steerable Sheath should follow the Instructions for Use and any training provided prior to the ablation procedure.

Use caution with any sheath advancement to ensure no air emboli is introduced into the left atrium.

3.3.7 Cryoablation Balloon Catheter Preparation

Preparation and deployment of the Cryoablation Balloon Catheter should follow the Instructions for Use and any training provided prior to the ablation procedure.

3.3.8 Mapping and Ablation

The objective of this clinical study is to evaluate the long-term safety and performance of the Cryterion Cardiac Cryoablation System.

The following is a stepwise approach to the AF ablation procedure that is recommended, and a flow diagram is provided in Figure 1:

Navigation and Placement of the Cryoablation Balloon Catheter

To use the Cryterion Cryoablation Catheter for a cryoablation procedure, follow these steps. (For more detailed instructions on the use of the Cryterion Cryoablation Console, refer to the Operator's Manual.)

1. Under fluoroscopic guidance, advance the circular mapping catheter/ balloon to the proximity of the target pulmonary vein.

2. Inflate the Balloon while remaining outside the target pulmonary vein.

3. To occlude blood flow, advance the balloon as necessary to occlude flow but remain outside the tubular portion of the vein.

4. Verify balloon position for complete PV occlusion with fluoroscopy and contrast injection diluted as a 50% to 50% solution.

Apply Cryo Energy until Isolation is Achieved and Documented with the Circular Mapping Catheter

1. Perform the cryoablation. A freezing cycle of ≥ 120 seconds is required. If PVI occurs in ≤60s, then an ablation cycle of 180s is performed; if PVI occurs in ≥60s, then an ablation cycle of 240s is performed.
    i. If the esophageal temperature falls below 25°C during an ablation cycle, the clinician can immediately abort the cryoablation.

ii. If there is loss of phrenic nerve capture, the clinician can immediately abort the cryoablation.

2. Record the point in time and temperature achieved when the PV appears isolated as evidenced by loss of PV signal on the Circular mapping catheter.

3. At the completion of the cryo application, wait for the thawing phase to complete before any balloon manipulation.

4. During the Thawing Phase, observe the console temperature indicator and activate the "push button" on the handle once the temperature has reached $+20^{O}$ C to deflate the balloon. When the temperature exceeds $+10^{O}$ C, advance the blue button on the catheter handle. Maintain pressure on the push button until the balloon deflates. The balloon deflates automatically when the temperature reaches 20^{O} C.

5. As needed, reposition the cryo balloon and re-apply cryo energy in the same vein.

6. Position the cryo balloon into the next targeted vein ostium and repeat the same steps for positioning, cryo application and thawing.

7. After treatments of all targeted veins have been completed and when the balloon is completely deflated, retract the catheter/ circular catheter/ guidewire into the sheath.

8. Final confirmation of all PVIs must occur before the end of the index procedure following the last cryo application for each targeted vein.

9. In the event, a vein is not considered isolated during the index ablation procedure or during the 90-day blanking period, additional cryo applications may be completed or the investigator may elect to use a market-approved device (RF or Cryo focal catheter) to complete the isolation of the target vein.

10. Following confirmation of PVI, the Cryoablation Balloon Catheter and Circular mapping catheter may be removed from the left atrium, but the sheath should be adequately flushed and left in place.

Reconfirm Isolation with the Circular Mapping Catheter

Reconfirmation of the PVI with the PolarMap Mapping Catheter should be completed by placing the catheter in each targeted PV and demonstrating electrical isolation. Pacing maneuvers to aid in the documentation of isolation (block) should follow the institution's standard-of-care. If IV medications are used in the confirmation process, the drug and dose should be documented on the eCRF. Final documentation for each targeted PV isolation shall be recorded on the EP recording system. Final tracings from the EP recording system shall be printed and used as procedure source documents.

AF Reinduction

Use of IV medications or pacing maneuvers attempting to re-induce the atrial fibrillation is at the discretion of the investigator. Drugs and dosages used shall be recorded on the eCRF.

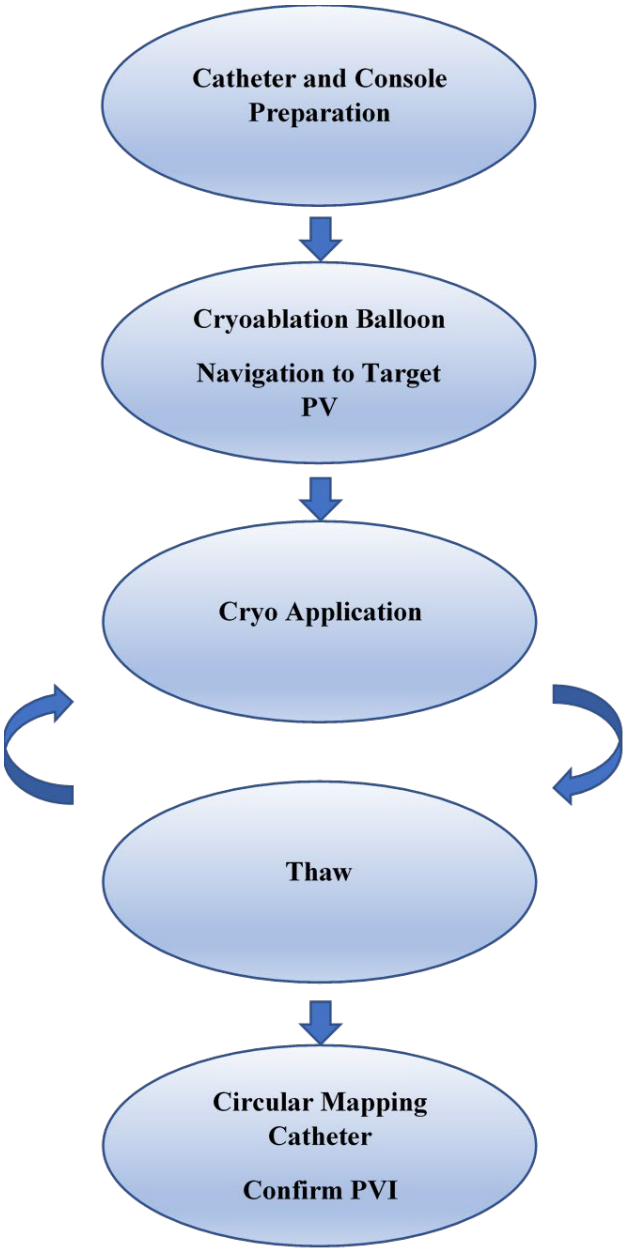

Figure 1: Atrial Fibrillation Ablation Procedure Flow Diagram

3.3.9 Procedure Data Collection

Collection of data generated during the procedure shall include (original document source to be kept at the site):

- Any change in health or cardiac medications prior to the ablation procedure
- EP system recording of 12-lead ECG at procedure start
- EP system recording of 12-lead ECG at procedure completion
- Total procedure time (from first venous access to time of last catheter removal from the left atrium)
- Total fluoroscopy time
- Recording of ablation summary data (including all cryo applications parameters per vein)
- Recording of all DCCVs delivered during the procedure
- Recording of all AADs administered during the procedure
- Recording of ACT values and Heparin administration
- Recording of any medications administered for anticoagulation reversal
- Ablation time to complete PVI using the Cryoablation System
- Baseline and final tracings using a PolarMap Mapping Catheter from the EP recording system documenting PV isolation (Submitted as procedure source notes)
- EP recording confirming PV isolation of all treated veins using an approved mapping catheter
- Documentation of System performance as described by the operator(s) using the System Performance Questionnaire. The system performance questionnaire will be used with all new clinical users for the first five (5) cases performed with the Cryterion System. After the first 5 cases, users can use the questionnaire to provide specific product feedback related to user experience(s) on an as needed basis (for example: the ability of

the cryoablation system to deal with tortuous anatomy of the LA/PVs).

Documentation of Cryoablation Balloon and Circular Mapping Catheter performance including:

- Catheter Preparation
- Catheter Access to Cardiac Locations
- Catheter Visualization
- Catheter Performance
  - Maneuverability
  - Torque-ability
  - Trackability
  - Durability

Additional data from the Cryoablation System may be transferred to the sponsor, stored and evaluated by sponsor personnel (including research engineers) for use in the continued development of the devices. All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential by the sponsor and all usage will be in full compliance of Cryterion Quality Assurance Procedures (QSPs) for protection of human subject and consistent with ISO 14155:2011, Section 6.5.

3.3.10 Device Returns

Any product failures will be reported to the Sponsor and the product will be returned to the sponsor for further analysis.

3.4 Follow-Up Procedures

All subjects will be followed for 12 months after their index ablation procedure. Each subject will undergo repeated assessments at 1, 3, 6 and 12 months. During the 90-day blanking period, subjects can undergo one repeat cryoablation procedure with the recommendation that all repeated ablations use the same cryoablation method or the investigator may elect to use a market-approved device (RF or Cryo focal catheter) without penalty regarding the primary effectiveness endpoint.

3.4.1 Hospital Discharge

The discharge visit will occur 7 days after index procedure or at the patient's discharge date, whichever comes first.

The subjects may be monitored with telemetry prior to hospital discharge for the documentation of recurrence of any atrial tachyarrhythmias and according to center practice.

The following evaluations shall be completed prior to discharge:

- Physical exam
- Medication changes
- Evaluation of Adverse Events
- 12-lead electrocardiogram

Careful attention shall be placed in the identification of potential cardiac effusions and post-procedure cardiac tamponade. Unexplained reduction in blood pressure, chest pain or shortness of breath may require a post-procedure TTE with further evaluation and management as per site's standard of care.

3.4.2 Visits at One Month (30 +/- 7 days) after the Start (Procedure) Date

The following evaluations will be performed during the one-month clinic follow-up visit. Data will be recorded on the Follow-Up eCRF.

- Physical exam
- Medication changes
- Arrhythmia Recurrence and treatment if any
- Adverse events assessment
- 12-lead electrocardiogram

3.4.3 Three Month (90 +/- 14 days) after the Start (Procedure) Date (designation in days required by Blanked Follow-Up Period and outcome measures)

The following evaluations will be performed during the 3-month clinic follow-up visit. Data will be recorded on the Follow-Up eCRF.

- Physical exam
- Medication changes

- Arrhythmia Recurrence and treatment if any
- Adverse events assessment
- 12-lead electrocardiogram
- 24 Hour Holter/ Cardiac Monitor Patch

3.4.4 Six Month Visits (180 +/- 30 days) after the Start (Procedure) Date

The following evaluations will be performed during the 6-month clinic follow-up visit. Data will be recorded on the Follow-Up eCRF.

- Physical exam
- Medication changes
- Arrhythmia Recurrence and treatment if any
- Adverse events assessment
- 12-lead electrocardiogram
- 24 Hour Holter/ Cardiac Monitor Patch

3.4.5 Twelve Month Visits (360 +/- 30 days) after the Start (Procedure) Date

The following evaluations will be performed during the 12-month clinic follow-up visit. Data will be recorded on the Follow-Up eCRF.

- Physical exam
- Medication changes
- Arrhythmia Recurrence and treatment if any
- Adverse events assessment
- 12-lead electrocardiogram
- 24 Hour Holter/ Cardiac Monitor Patch

3.4.6 Unscheduled (additional) Visits

Any visit outside of the scheduled follow-up visits will be considered an Unscheduled Visit. These visits will include “return to clinic visits” for analysis of any clinical complications or preparation for a DCCV. All pertinent data will be recorded on an unscheduled visit eCRF.

this should include:

- Physical exam
- Medication changes
- Arrhythmia Recurrence and treatment if any
- Adverse events assessment
- 12-lead electrocardiogram

Table 2: Follow-Up Schedule

	Screening & Baseline	Index Procedure Day 0[2]	Discharge (0 to 7 days)	1 month (30 ± 7 days)	3 months (90 +/- 14 days)	6 months (180 +/- 30 days)	12 months (360 +/- 30 days)	Additional visit	Additional Procedure (> Day 0)
CIP Informed Consent	X								
Eligibility Review	X								
Medical History	X			X					
Physical Exam	X		X	X	X	X	X	(X) optional	
Medications	X	X	X	X	X	X	X	(X) optional	X
Transthoracic Echocardiogram (TTE)	X								
CT scan, Trans Esophageal Echo (TEE) or intracardiac echo (ICE) to R/O LA Thrombus		X (CT/TEE within 72 hours of procedure)							(X) Following Procedural Standard of care
CT scan, ICE or Pulmonary Venogram to r/o common ostium or enlarged PV diameter[1]	(CT scan)	ICE or (Pulmonary Venogram)							
Device data		X							X
Adverse Events	X	X	X	X	X	X	X	(X) optional	X
12-lead ECG	X	X	X	X	X	X	X	(X) optional	X
24 Hour Holter/Arrhythmia Patch					X	X	X	(X) optional	
Labs (per SOC)	X								
HCG (female subjects of child bearing potential)	X								

[1]Only one of these tests is required to establish common PV ostium and/or enlarged PV diameters

[2]All subsequent visits are counted in days from the index procedure

4 STATISTICAL METHODS

4.1 Analysis Population

The analysis of the endpoints of the study will be based on the Enrolled Subject Population.

4.2 Statistical Analysis for the Study Outcome Measure

Analysis of the primary endpoints will be performed on an intent-to-treat basis. All partial data that is available on subjects who drop out during the course of the study will be included.

Descriptive analysis will be used to present the study. Continuous variables will be reported as median and range, mean ± standard deviation; categorical variables will be reported as n/N (%).

The primary safety endpoint outcome is freedom from a composite MAE comprised of the device or procedure related adverse events as listed in the Primary Endpoints section of the protocol. The primary safety endpoint will be assessed in all screened subjects who undertake the ablation procedure to the point that the Cryoablation Balloon is inserted into the subject.

Additionally, the study will compare the study device safety outcome rate to a rate derived from available literature data. The study outcome rate will be presented along with rates from previous studies on market approved devices and a descriptive comparison will be made.

The primary performance endpoint is acute success defined as rate of successful pulmonary vein electrical isolation with confirmation of entrance/exit block. Any screened subject who undertakes the ablation procedure to the point that the Cryoablation Balloon is used to deliver at least one cryo application will be used to assess the primary and the additional effectiveness endpoint.

All study results will be analyzed using widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of baseline and operative characteristics and outcome results will be provided. Additionally, all adverse events will be summarized by type of event, severity, relationship to the device and/or procedure, and timing of event relative to the procedure date.

The following will be included in the Clinical Study Report:

- Summary of complications will be completed and included in the interim report.
- Design, methods, procedure, sample size
- Criteria for the termination of the clinical investigation on statistical grounds,
- Analysis of endpoints
- Analysis of Adverse Events and Outcomes

4.3 Study Size Justification

[redacted]

5 ADVERSE EVENTS

Any adverse event (AE) that occurs in a subject once they are enrolled in the study is considered a reportable event.

Any medical conditions, problems, signs, symptoms, and findings occurring prior to treatment are to be reported as pre-existing conditions on the Medical History eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation

Adverse events are categorized as defined in ISO 14155: 2011 and MEDDEV 2.7/3.

Adverse event (AE): Any untoward medical occurrence unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational medical device or comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.

Adverse device effect (ADE): Adverse event related to the use of an investigational medical device.

Note 1: this definition includes any event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

Note 2: this definition includes any event that is a result of a user error or intentional abnormal use of the investigational medical device.

Serious adverse event (SAE): Adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject as defined by either:
    a. a life-threatening illness or injury
    b. a permanent impairment of a body structure or a body function
    c. in-patient hospitalization or prolongation of existing hospitalization,
    d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.

Serious adverse device effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE): 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.

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of USADEs and SAEs as required by local/regional regulations.

With any procedure or treatment, there are known possible risks and complications. A list of known or anticipated adverse events for the Cryoablation System is found in the Investigator Brochure.

Unanticipated Serious Adverse Device Effects (USADEs)

Investigators are required to submit a report to the Sponsor as soon as possible of any suspected Unanticipated Serious Adverse Device Effect (USADE) occurring during an investigation on the Adverse Event eCRF, but in no event later than one (1) business days after the Investigator first learns of the effect.

When an Investigator suspects that an event meets the definition for a USADE, the event, date of onset, seriousness, severity, duration, treatment, outcome and relationship to device will be recorded on the Adverse Event eCRF.

The Sponsor/ manufacturer must then conduct an evaluation of the suspected USADE and maintain records of the evaluation.

5.1 Adverse Event Reporting requirements

The Investigator is responsible for reporting all adverse events that occur during the study. Initial reporting will be with the Adverse Event eCRF; however, additional information may be required by the Sponsor, the independent medical monitor, the Ethics Committee, or any other regulatory authority. The Investigator shall report any serious adverse events (SAEs), serious adverse device effects, (SADEs), or unanticipated serious adverse device effects (USADEs) to the Sponsor as soon as possible after becoming aware of the event, but not later than reporting timelines listed in table 3 below. All SAEs, SADEs, and USADEs will be documented on the Adverse Event eCRF along with an explanation of any medical treatment administered. Documentation shall include the time of onset, complete description of the event, severity, duration, actions taken and outcome. Recurrence of atrial fibrillation (or other atrial tachyarrhythmias) is not considered an adverse event as there is a known recurrence rate associated with AF ablation, unless associated with worsening subject's conditions. This would include scheduled hospitalizations to treat these arrhythmias (e.g., pharmacologic and/or electrical cardioversion or re-ablation after blanking period). All recurrences will be

reported on the follow-up eCRF. In the event an arrhythmia recurrence resulted in hospitalization for other clinical symptoms, an adverse event shall be recorded and reported. In the event that an alternative method of reporting is necessary (i.e. the eCRF system is unavailable), please report the adverse event or device experience to the sponsor by sending the notification form to the following email address:

[redacted]

Table 3: Investigator reporting requirements:

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Subject death during the study	Complete information in EDC page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event.
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete information in EDC page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Reporting required through the end of the study
Serious Adverse Event	Complete information in EDC with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
Serious Adverse Device Effects	Complete information in EDC with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
Adverse Event including Adverse Device Effects	Complete information in EDC with all available new and updated information.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through the end of the study
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)	Complete EDC with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event.

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.		• Reporting required through the end of the study

5.2 Event Relationship to the Device

The Investigator shall provide information regarding the relationship of the event to the Cryoablation System and the AF ablation procedure. The AE relationships are defined in Table 4 below:

Table 4: AE Relationships

Not Related	The cause of the AE is known and is not related to any aspect of the ablation portion of the AF procedure.
Unlikely related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	There is a reasonable possibility that the event may be related to the ablation portion of the AF procedure. The AE has a timely relationship to the study procedure; however, it follows no known pattern of response and an alternative cause seems more likely or there is significant uncertainty.
Probably Related	It is probable that the event was related to the ablation portion of the AF procedure. The AE has a timely relationship to the study

	procedure and follows a known pattern of response, but a potential alternative cause may be present.
Causal Related	The event was definitely related to the ablation portion of the AF procedure. A related event has a strong temporal relationship and an alternative cause is unlikely.

5.3 Death Notice

When a site becomes aware of a subject's death, regardless of cause, it should be reported to the Sponsor as soon as possible but no later than three (3) calendar days. Notification shall be made to the reviewing EC per local requirements.

The materials to be submitted to the Sponsor for a death include the following:

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Whether or not the death was witnessed
- An assessment by the Investigator as to whether the death is related to study interventions.
- A copy of the subject's death certificate If available
- When applicable, a copy of an autopsy report. If available

For reported deaths, the Investigator or designee shall supply the Sponsor and the presiding EC with any additional requested information, if available (i.e., hospital records).

5.4 Device deficiencies.

Device Deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented on the device experience CRF within 3 calendar days of first becoming aware of the event. Device failures and malfunctions should also be

documented in the subject's medical record. Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF. Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

Any trends for complaints related to subject adverse events will be assessed by the sponsor.

5.5 Clinical Events Committee (CEC)

There is no CEC in place for this study. The Sponsor (or designee) will coordinate the convening of meetings to review all safety events reported in the study database. Based on this review, the Sponsor may make recommendations regarding all aspects of the conduct of the study, including the termination of the study. All recorded minutes of the meetings and actions will be kept on file and available for review as requested. The Sponsor may consider seeking the input of a Clinical Event Monitor (CEM, independent physician expert in the electrophysiology space) for additional recommendations regarding specific aspects of the conduct of the study. Additional source documentation will be requested as needed to the site.

6 RISK-BENEFIT ANALYSIS

6.1 Risks

The following adverse events are associated with AF mapping and ablation procedures using cryo energy:

- Air embolism/N_2O embolism
- Anemia
- Anesthesia reaction
- Arrhythmias
- Arteriovenous (AV) fistula
- Atrial esophageal fistula
- Myocardial infarction
- Obstruction, perforation or damage to the vascular system
- Pericardial effusion
- Pericarditis
- Phrenic nerve damage
- Pleural effusion

- Cardiac perforation/tamponade
- Cardiac thromboembolism
- Cerebral infarct (hemorrhagic or thromboembolic)
- Chest pain/discomfort
- Complete heart block (transient or permanent
- Congestive heart failure
- Coronary artery spasm/dissection
- Coronary artery thrombosis/occlusion
- Death
- Diaphragmatic paralysis
- Elevated cardiac enzymes
- Endocarditis
- Fever
- Heart failure/pump failure
- Hemothorax
- Infection/sepsis
- Local hematomas/ecchymosis
- Major bleeding, requiring surgery or transfusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Pulmonary hypertension
- Pulmonary vein dissection
- Pulmonary vein stenosis
- Pulmonary vein thrombosis
- Radiation injury
- Respiratory depression
- Skin burns
- ST segment elevation
- Temporary complete heart block
- Thromboembolism
- Transient ischemic attack (TIA)
- Valvular damage/insufficiency
- Vasovagal reaction

6.2 Benefits

The Cryterion Cardiac Cryoablation System provides the benefit of creating endocardial necrosis using cryo energy delivered to targeted pulmonary veins in the management of atrial fibrillation. Unique System design changes including those to the Cryoablation Balloon Catheter, may increase the likelihood of safely applying the energy, increasing the durability of the PVI, and aiding in more accurate determination of electrical isolation of the vein(s).

6.3 Mitigation of Risks

Subject risk will be minimized through the investigator selection process, investigator training and subject selection procedures.

Benchtop studies and pre-clinical research have demonstrated that the System is safe for human use. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels. The sponsor believes that the potential benefits of the system outweigh the potential risks. The current amendment to the CE Mark Study is designed to follow the investigator's standard of care for AF ablation subjects and evaluate the long-term effectiveness and safety of the System. The subject data from the amended CE Mark Study will be retrospectively included in a subsequent Post Market Clinical Follow-Up study to collect long-term system-related, clinical and subject reported outcome data for the Cryterion Cardiac Cryoablation System.

Additionally, study risks shall be minimized by:

- The use of standard medical grade materials that have been thoroughly characterized and tested to assure biocompatibility
- Extensive pre-clinical evaluation including in vitro bench testing and animal study
- The well-established, standard nature of the intra-cardiac procedures and techniques to be used

7 DATA QUALITY ASSURANCE

The sponsor will oversee the database for this study in accordance with regulatory data integrity requirements, the Data Management Plan (DMP), and corporate QSPs. Data will be collected and entered on the eCRFs in the database. Data will be reviewed for accuracy and completeness by the sponsor (or designees) during all onsite and remote monitoring visits, and throughout the data management process. Any discrepancies will be resolved with the Investigator or designees, as appropriate. To preserve data integrity and security of the database, access to the database will be controlled by the sponsor (or designees) and shall be limited to appropriately trained personnel with assigned log-on credentials.

7.1 Data Management

The standard procedures for handling and processing records will follow the sponsor (or designee) QSPs for data management. All data collection will be in compliance with Good Clinical Practice (GCP). A comprehensive Data Management Plan (DMP) will be developed for the clinical study.

For the duration of the study, the Investigator and their designees will maintain complete and accurate documentation, including, but not limited to, medical records, study progress notes, laboratory reports, signed subject informed consent forms, device

accountability logs for the investigational product (i.e., Cryoablation System components), correspondence with the reviewing EC, correspondence with the sponsor (or designees) and study monitors, adverse event reports, and information regarding subject discontinuation/withdrawal or completion of the study.

The Investigator/ Institution will permit direct access to source data and documents to complete study-related monitoring, audits, EC reviews, adverse event adjudication and regulatory inspections that may be performed. The Investigator will obtain, as part of the informed consent process, permission for authorized Sponsor employees, study monitors or regulatory authorities to review, in confidence, any records that identify subjects in this study.

7.2 Subject Identification

Subjects will be identified on all eCRFs and source documents by a unique identification reference, which will be issued once the Informed Consent has been signed and date of signature has been entered in the database. An identification reference shall not be reused for any reason.

7.3 Screen Failure Subjects

Subjects who are screened for the study but are not enrolled for any reason will not be followed and their data will not be used for any outcomes analysis.

7.4 Subject Study Completion and Withdrawal

A subject will be considered to have completed their participation in the study when the 12-month visit data collection is complete and submitted. Subjects who withdraw for any reason will have all available data entered into the database. Reasons for withdrawal will be entered on the Study Exit eCRF.

7.5 Subjects Lost-to-Follow-Up

A subject will be considered lost-to-follow-up if any of the follow-up visits through 12 months is missed and all reasonable efforts have been made to contact the subject to request their return for the study visit. All attempts to contact the subject will be documented on the Study Exit eCRF.

7.6 Confidentiality of Data

Information regarding study subjects will be kept confidential and managed according to the requirements and regulations of local and national governing bodies, ISO 14155:

2011, Section 6.5, EU 536/2014 and QSPs of Cryterion Medical or participating Contract Research Organizations (CROs).

All data and information collected during this study will be considered confidential by the sponsor and their delegates. All data used in the analysis and summary of this study will be anonymous and without reference to specific subject names. Access to subject files will be limited to authorized personnel of the sponsor (including core labs), their designees, the Investigator, Clinical Site research staff and authorized Regulatory Authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study.

7.7 Source Documents

Source data encompasses all information, original records of clinical findings, observations, or other activities, which are required in a clinical study for the reconstruction and evaluation of the study. Examples of these original documents, and data records include, but are not limited to, hospital records, clinic and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, copies of clinic and procedural site coding and billing records, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, and at the laboratories involved in the clinical trial.

Regulations require that the Investigator maintain information in the subject's medical records that corroborate data collected for the study. To comply with these regulatory requirements, the following is a list of information that shall be maintained, at a minimum:

Medical history/ general physical condition of the subject before involvement in the study, which will be of a sufficient nature to verify the protocol eligibility criteria.

Study/ progress notes, including the date of entry into the study, documenting the following:

- The general health of the subject.
- The discussion of the study risks and benefits with the subject.
- Completion of the informed consent process.
- A statement that the subject reviewed and signed the subject informed consent form.

- Dated notes from each subject visit to support all data recorded on the eCRFs.
- Adverse Events reported and their continuation or resolution at each visit, including supporting documentation, such as discharge summaries, lab results, non-invasive testing reports, etc.
- Notes regarding protocol-required and prescription medications taken during the study (including start and stop dates, dosage, and routes of administration, if known).
- Subjects general health and medical condition upon completion of or withdrawal from the study.

7.8 Electronic Case Report Forms (eCRFs)

This study will use Case Report Form worksheets and an electronic Case Report Form (eCRF) as the primary data collection instruments and will record data by electronic capture. All data requested on the eCRF must be entered in a timely manner. If a data entry error has been made, the corrected information will be entered on the eCRF. All such changes are recorded in the audit and queries report.

Additional device/ procedure data related to the performance during a cryoablation procedure is collected within the Cryo Console. These data may be downloaded on a per-subject basis and printed for use as a supporting source document to the procedure eCRF.

Specific guidelines to complete the eCRFs will be provided to the Investigator and other site personnel, as appropriate. The Investigators (and designees) are responsible for reporting clinical study-requested information in the eCRFs.

7.9 Records Retention

The Investigator will retain study-essential documents for ten (10) years after formal closure or discontinuation of the trial. These documents must be retained for a longer period if required by an agreement with the sponsor or defined by local or national regulations. The sponsor will inform the Investigator/ Institution as to the date of formal closure or discontinuation of the trial and when these documents no longer need to be retained.

7.10 Clinical Monitor

A Clinical Trial Monitor (or designee) will be assigned as the clinical monitor for this study. The personnel will be qualified by training and experience to oversee the conduct of the study. The Clinical Monitor's responsibilities include maintaining regular contact with each investigational site through telephone contact and on-site visits to ensure that:

- The CIP and the defined visit schedule is followed,
- Complete, timely, and accurate data are submitted,
- Issues with inconsistent and incomplete data are addressed;
- All Device Experiences, AEs, SAEs and UADEs are reported to the Sponsor,
- The site facilities continue to be adequate.

Any questions regarding these matters should be addressed to the Clinical Affairs department of the sponsor. Monitoring of the conduct and data produced from the clinical study will be assigned to the Clinical Trial Monitor (or designee).

7.11 Clinical Data Monitoring Procedures

Clinical Trial Monitors (or designees) will conduct site visits at the study facilities to monitor the study, which will be compliant with the CIP, QSPs, and the Clinical Monitoring Plan (CMP) and applicable regulations. Monitoring visits will occur as defined in the CMP. The Investigational site agrees to allow these monitors and other authorized sponsor personnel access to information and clinical supplies related to the study. The Cryterion Medical monitors (or designees) will review source data and verify data entered into the eCRFs against hospital/ clinic records and/or other source documents, to ensure accuracy and completeness of the eCRFs for each subject. Clinical Investigators and their staff agree to assist the monitors in their activities. Requests may be made to review subject charts by sponsor personnel and/ or designee(s) so that protocol adherence and source documentation can be verified.

Monitoring visits will be performed at regular intervals throughout the course of the study to ensure compliance with the protocol. Monitoring activities may include, but are not limited to:

- Evaluation of subject screening and selection methods
- Verification of signed ICF for each subject

- Verification of source documentation against completed eCRFs and worksheets for each subject
- Source data review to ensure proper reporting of all reportable events
- Assurance that required study reports, including reports to the applicable EC, are generated in a timely manner
- Monitoring of Safety Events, including device deficiencies that may have led to an SAE
- Monitoring of device experiences, irrespective of associated safety events
- Review of device accountability records and device reconciliation
- Review of protocol deviations
- Overall study compliance
- Review of the Investigator Site File (ISF)

7.12 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), ISO 14155: 2011, applicable regulatory requirements, and institutional procedures.

7.13 Deviations from the Clinical Investigational Plan

A protocol deviation is defined as an event in which the Investigator or site personnel deviates from the study protocol or study procedures. It is the Investigator's responsibility to ensure that there are no deviations from the protocol. On a rare occasion, a sponsor-approved deviation to a screening test, exclusion criteria, or protocol-specific procedure may be granted in advance by the sponsor and must be reported in full compliance with all established procedures and conditions of the reviewing EC.

An Investigator may deviate from the protocol without prior written approval from the sponsor in cases of medical emergencies to protect the life or physical well-being of a subject. In the event of an emergent deviation, the Investigator is required to notify the sponsor and the applicable EC as soon as possible, but in no event later than five (5) business days after the occurrence of the deviation from the protocol.

Except in such an emergency, prior approval by the sponsor is required for changes in, or deviations from, the CIP/ protocol. Additionally, if these changes or deviations affect the scientific soundness of the investigational plan or the rights, safety, or welfare of human subjects, EC notification is required.

Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., the subject was not available for a scheduled follow-up office visit or has moved without providing a forwarding address). These events, although outside the Investigator's control, are still required to be reported on the appropriate Protocol Deviation eCRF to ensure that all deviations from the standard subject population are adequately documented and reported. The Investigator will inform the sponsor and the reviewing EC of all protocol deviations as per the EC requirements established for this study.

If the sponsor becomes aware that an Investigator is not complying with the any part of the CIP, including the signed Investigator Agreement, the protocol, or any conditions of approval imposed by the reviewing EC, the sponsor will first try to secure compliance, and may suspend the Investigator's participation (including enrollment at the site) in case of failure to implement remedial actions. The sponsor may terminate an Investigator's participation in the study at its discretion.

7.13.1 Maintaining Records

The Investigator will maintain the following accurate, complete, and current records related to the Investigator's participation:

Correspondence with another Investigator, an EC, Cryterion Medical, a Sponsor monitor or designee, or any regulatory agency.

Records of each subject's case history and exposure to the device, including:

- Source records evidencing each eligibility criterion to enroll in the study
- Documents evidencing informed consent and for participation in the clinical study without informed consent,
- Any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent,
- All relevant observations, including records concerning adverse device effects (whether anticipated or not),

- Information and data on the condition of each subject upon entering, and during the investigation, including information related to relevant previous medical history and the results of all diagnostic tests,
- A record of the procedure involving treatment with the CryoAblation System for each subject, including the date and time of the procedure.
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

7.13.2 Submitting Reports

In compliance with local and national laws, each Investigator may be required to prepare and submit complete, accurate, and timely reports to the sponsor and/ or ECs. These reports may include:

- Any unanticipated adverse device effects or SAEs occurring during an investigation.
- Any deviation from the investigational plan emergently made to protect the life or physical well-being of a subject.
- A protocol deviation requiring prior written approval from Cryterion Medical (except in emergency situations). If the deviation affects the scientific soundness of the plan or the rights, safety, or welfare of subject, prior documentation of EC approval may be required.
- Any further information requested by an EC about any aspect of the investigation.

The Investigator will provide, in writing, any withdrawal of EC approval of the study or an Investigator within five (5) business days of such action.

7.14 Sponsor's Responsibilities

7.14.1 General Duties

The sponsor has the overall responsibility for the conduct of the study, including assurance that the study satisfies the regulatory requirements of the appropriate regulatory agencies, ensuring EC approvals, selecting Investigators, ensuring proper monitoring and that informed consent was obtained by the principal investigator or authorized designee. The sponsor will provide all information necessary to conduct the

study, including the Clinical Study Protocol, and any reports of prior investigations, as appropriate. During the conduct of the clinical study, updates regarding information that may impact the clinical study will be made available to all appropriate national and local regulatory authorities.

7.14.2 Selection of Investigators

The sponsor will select Investigators (including co-Investigators performing the procedure) qualified by training and experience. Sites will be selected based on a site assessment, appropriate facilities, clinical experience and the qualifications of the Principal Investigator. Investigators will be evaluated by the sponsor based on:

Curriculum vitae, or other statement of Investigator's relevant training and experience, including type of experience with the intended procedure and clinical research, specifically,

Education and experience in the ablation management of arrhythmias,

Whether the Investigator has an adequate subject population to meet requirements of the study enrollment,

Whether the Investigator has adequate time to be personally involved in the conduct of the study, and adequate research staff and resources to support the study,

Whether the Investigator's Study Center is associated with an EC that satisfies all applicable regulatory requirements,

Whether an Investigator was involved in an investigation or other research that was terminated. This may require an explanation of the circumstances that led to the termination.

Prior to study initiation, each Investigator must also submit a:

- Certificate of human subject's protection training (if required by the reviewing EC)
- Certificate of GCP training,
- Signed Investigator's Agreement, indicating an Investigator's commitment to:
    - Conduct the investigation in accordance with the agreement, the CIP/protocol, GCP, and any conditions of approval imposed by the EC,

- Supervise all testing of the device involving human subjects,
- Ensure that the requirements for informed consent are met,
- Conduct the study according to the CIP/protocol.

The Sponsor reserves the right to apply additional criteria to site and/or Investigator selection.

7.14.3 Training

The Sponsor will provide technical training on all components of the Cryoablation System prior to enrolling any subject. Training may consist of a review of the IFU, hands-on training on the device and procedure, presentations, literature, etc, and/or providing clarifications to site personnel concerning the operation of study equipment/devices. The training program will be standardized and will be documented. Additional training will include a review of the protocol, the regulations for medical device investigations and general study logistics required to complete the study.

At the request of the investigator and while under investigator supervision, Sponsor personnel may support equipment operation during the ablation procedure or additional procedures, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following:

• Operating, support preparation and setting the Balloon Catheter system to adjust parameters to investigator-requested settings.

• Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel

• Entering data on technical source form as long as the responsible investigator verifies and signs the completed worksheet.

• Print out/download programming reports/parameters directly from the EP equipment and provide original printouts or electronic data reports to clinical site as source documentation.

• Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

Sponsor personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

Training of appropriate clinical study personnel will be the responsibility of the sponsor (or designee). To ensure uniform data collection and protocol compliance, the sponsor will review the CIP/protocol (including the ICF), techniques for identification of eligible subjects, instructions on data collection, methods for scheduling follow-up visits within the visit window, etc. Detailed feedback regarding completion of the eCRFs, study requirements, and protocol compliance will be provided by the sponsor, its study monitors, and/ or designees, functioning in a data management capacity.

7.14.4 Changes in the Clinical Investigational Plan

The sponsor will obtain appropriate regulatory approval for any change to the CIP/ protocol that may affect the scientific soundness of the investigation or the rights, safety and/ or welfare of the subjects.

The sponsor will provide approved protocol amendments to the Investigators prior to implementing the amendment. The Investigator (or Sponsor designee) will be responsible for notifying the reviewing ECs of the protocol amendment (administrative changes) or obtaining EC approval of the protocol amendment (changes in subject care of safety), according to the instructions provided with the protocol amendment. The EC acknowledgement/ approval of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must be provided to the sponsor and placed in the Trial Master File (TMF).

7.14.5 Withdrawal of Regulatory Approval

The sponsor will notify all reviewing ECs and participating Investigators of any withdrawal of regulatory approval to conduct the clinical study and shall do so within five (5) business days after receipt of notice of the withdrawal of approval.

8 ETHICS AND REGULATORY COMPLIANCE

8.1 Conduct of the Clinical Study

Conduct of the clinical study will follow QSPs from Cryterion Medical, as well as the Declaration of Helsinki, Good Clinical Practices, ISO 14155: 2011, and other regional and local laws. Each Investigator must sign and date the Investigator Agreement prior to the start of this study. With the signature, the Investigator agrees to perform all study procedures according to the governing local and national regulations and the Clinical Investigational Plan.

8.2 Ethics Committee Approval

A properly constituted, valid EC must review and approve the CIP, ICF, and related subject information and recruitment materials prior to initiation of the study. It is the responsibility of the Investigator (or Sponsor designee) to obtain protocol approval from the institution's EC, and to keep the EC informed of any serious adverse events or serious adverse device effects and amendments to the protocol. Additional requirements imposed by the EC or other regulatory authority shall be followed as appropriate. All correspondence with the EC shall be filed in the ISF and copies sent to the sponsor (or designees).

8.3 Clinical Study Informed Consent Approval

In accordance with the principles of Informed Consent, the Declaration of Helsinki, Good Clinical Practice (GCP), and ISO 14155: 2011, informed consent will be obtained and documented in writing before a subject is enrolled in the clinical study.

It is the responsibility of the Investigator to ensure that a written informed consent is obtained from the subject (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care. Information obtained during the conduct of the clinical study that may impact the subject informed consent may require revisions to the informed consent. If so, revisions and approvals of such changes by the appropriate regulatory authority is required. Documentation of the current versions of the informed consent will be filed in the clinical study TMF.

8.4 Identification and Confidentiality

Subject identification and confidentiality will be ensured in accordance with all applicable regulatory and EC governance. This includes, but is not limited to, the following:

- Subjects will be identified on all eCRFs and source documents by a unique identification reference.
- eCRFs are confidential documents and will only be made available to Cryterion Medical (or designees), the Investigator, the biostatistician, the Clinical Events Monitor (CEM), and, if requested, to advisory committees and regulatory authorities (including US FDA).
- Data will be stored and analyzed by computer following national regulations for handling of computerized data.
- Each Study Center will maintain (anonymous to Cryterion Medical) a list identifying all subjects entered into the trial. The list will be maintained as part of the ISF and monitored for completeness.

8.5 Site Qualification Visits

A site qualification visit (SQV) will be performed to evaluate site facilities, Investigator qualifications, and site knowledge of Good Clinical Practice (GCP) guidelines. Cryterion Medical's QSP for SQVs will be followed and a report filed in the Trial Master File (TMF), which will be maintained by the sponsor (or designee). If the site has been involved in previous sponsor research within the previous 12 months, the SQV may be waived in compliance with Cryterion QSPs.

8.6 Site Initiation Visits

All study personnel will be required to participate in a Site Initiation Visit (SIV), following Cryterion Medical's QSPs (or designee's QSPs). Components of the SIV may include:

- Introduction of the study design including the protocol-specific treatment and follow-up phase
- Informed Consent process
- Product training to all end-users
- eCRF completion training
- Safety reporting instructions
- Training on the regulations governing human research
- Procedure training on the use of the device

8.7 Insurance

The sponsor shall maintain insurance coverage for this study. Pertinent information regarding the coverage shall be made available to the site upon request.

8.8 Site Audit Plan

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices. The Investigator and/ or designee must be available to respond to reasonable requests and queries made by authorized regulatory representatives during the audit process. The Investigator must provide the sponsor with copies of all correspondence that may affect the review of the current study or their qualifications as an Investigator in this and future clinical studies conducted by the sponsor.

8.8.1 Site Data Audits by Sponsor

In accordance with local and national regulations and Sponsor's operating procedures, an internal audit may be requested to access all study records, including source documents, for inspection and duplication. The investigator will ensure the capability for inspections of applicable study-related functions.

Site data quality assurance audits may be conducted at various sites during the clinical study. Selection of sites to undergo auditing will be determined by the sponsor as needed.

8.8.2 External Audits

Participating study sites may receive requests from National regulatory agencies to conduct a site audit. The Investigator and/ or designee is required to report to the sponsor as soon as possible after receiving a request from a regulatory authority to perform an audit. The clinical Investigator agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

8.9 Device Traceability

The Cryoablation System components will be provided for the procedures and will be stored at each site or transported for the procedure. All sites will maintain a device accountability log for investigational devices used in the study. Commercially available products will not be tracked. At the end of the study, all unused study devices will be returned to the sponsor.

8.10 Public Domain Access to the Clinical Study

A description of this clinical trial will be available on http//www.Clinicaltrials.gov.

8.11 Required Reports

The sponsor will remain in compliance with all required and pre-specified reports during the enrollment and follow-up of the clinical study. EC requirements for reports, including all clinical study reports will be provided as requested.

9 GENERAL CONSIDERATIONS

9.1 Discontinuation of the Clinical Study

The Sponsor reserves the right to discontinue the study at any stage, with suitable written notice to the Investigator and the appropriate government regulatory agencies. Such decisions will be based on advice from the Scientific Advisory Board or Clinical Events Monitor. Similarly, Investigators may withdraw from the study, subject to providing written notification to the Sponsor, within 30 days of their intent to withdraw. However, the Sponsor and Investigators will be bound by their obligation to complete the follow-up of subjects already enrolled into the study.

as the sponsor, may terminate Investigator and site participation in the study if there is evidence of an Investigator's failure to maintain adequate clinical standards or evidence of an Investigator's or staff's failure to comply with the Clinical Investigation Plan/ protocol.

Notification of suspension or termination will occur no later than fifteen (15) business days after the sponsor makes the determination. In the event of study suspension or termination, the sponsor or designee will send a report to the reviewing EC, the appropriate regulatory agencies, and all participating Investigators, outlining the circumstances. Any suspension or termination may not be re-initiated without prior approval of the EC and the sponsor.

9.2 Use of Information and Publications

All information concerning sponsor's operations, patent applications, manufacturing processes, and basic scientific data supplied by the sponsor to the Investigator and not previously published, are considered confidential and remain the sole property of the sponsor. **This includes all study materials, CRF worksheets, eCRFs and any subject data collected during the conduct of this study.**

All parties shall observe data confidentiality rules during the course of the study. The privacy of each study subject and confidentiality of his/her information shall be preserved in reports and publication of any data.

The information developed in this study may be used by the sponsor as support for future regulatory filing(s) and in connection with the continued development of the Cryoablation System components. Any publication or other public presentation of the data resulting from this study will require prior review and written approval of the sponsor.

At the end of the study, it is expected that the sponsor and the Investigators will promptly prepare and submit a multi-center manuscript for publication in a reputable scientific journal. The publication of the principal results, including abstracts, from any single-site experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior written approval of the sponsor.

Further analyses, beyond those presented in the initial multi-center publication may be proposed to the sponsor. Many secondary manuscripts are anticipated. For purposes of timely abstract presentation and publication, such secondary publications may be delegated to the appropriate principal authors; however, final analyses and manuscript review for all multi-center data will require the prior written approval of the sponsor.

None of the results, in whole or part, of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the sponsor. Any Investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

10 BIBLIOGRAPHY

1. Chugh S, Havmoeller R, Narayanan K, et al. Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. CIRC. 2014;129(8):837-847.
2. Camm AJ, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*, 2012 Oct; 14(10):1385-413
3. Calkins H, Hindricks, G, Cappato, R, et al. 2017HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. Vol. 10, October 2017
4. Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. Oct 2010;31(19):2369–2429
5. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. Cardiovasc Res. May 2002;54(2):204–216.
6. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. Jan 10 2002; 415(6868):219–226.
7. Dobrev D, Voigt N,Wehrens XH. The ryanodine receptor channel as a molecular motif in atrial fibrillation: pathophysiological and therapeutic implications. Cardiovasc Res. Mar 1 2011;89(4):734–743.
8. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev. Jan 2011;91(1):265–325.
9. Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. J Clinical Invest. Aug 1 2011;121(8):2955–2968
10. Jais P, Haissaguerre M, Shah DC et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation. Feb 4 1997;95(3):572–576.
11. Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. Sep 3 1998; 339(10):659–666.
12. Everett TH 4th, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. Am J Physiol Heart Circ Physiol. Dec 2006;291(6):H2911–2923
13. Hindricks G, Willems S, Kautzner J, De Chillou C, Wiedemann M, Schepel S, Piorkowski C, Risius T, Kottkamp H; EuroFlutter Investigators. Effect of electroanatomically guided versus conventional catheter ablation of typical atrial flutter on the fluoroscopy time and resource use: a prospective randomized. J Cardiovasc Electrophysiol. 2009 Jul;20(7):734-40.

14. Sporton SC, Earley MJ, Nathan AW, Schilling RJ. Electroanatomic versus fluoroscopic mapping for catheter ablation procedures: a prospective randomized study. J Cardiovasc Electrophysiol. 2004 Mar;15(3):310-5.
15. Kottkamp H, Hügl B, Krauss B, Wetzel U, Fleck A, Schuler G, Hindricks G. Electromagnetic versus fluoroscopic mapping of the inferior isthmus for ablation of typical atrial flutter: A prospective randomized study. Circulation. 2000 Oct 24;102(17):2082-6.
16. Smeets JL, Ben-Haim SA, Rodriguez LM, Timmermans C, Wellens HJ. New method for nonfluoroscopic endocardial mapping in humans: accuracy assessment and first clinical results. Circulation. 1998 Jun 23;97(24):2426-32.
17. Cappato R, Calkins H, Chen SA, et al. Updated Worldwide Survey on the Methods, Efficacy, and Safety of Catheter Ablation for Human Atrial Fibrillation. Circ Arrhythmia Electrophysiology. 2010;3:32-38.
18. Sohn C, Williams S, Chubb H, et al. Catheter Contact Force: A Review of Emerging Techniques and Technologies in AF Ablation.
19. Natale A, Reddy V, Monir G, et al. Paroxysmal AF Ablation with a Contact Force Sensing Catheter. Journal American College of Cardiology 2014;64:647-56.
20. Reddy V, Dukkipati S, Neuzil P, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation. Circulation. 2015;132:907-915.
21. Barnett A, Bahnson T, Piccini J. Recent Advances in Lesion Formation for Catheter Ablation of Atrial Fibrillation. Circ Arrhythmia Electrophysiology, June 2016;9 e003299.
22. Packer D, Kowal R, Wheelan K, Irwin J, et al. Cryoballoon Ablation of Pulmonary Veins for paroxysmal Atrial Fibrillation. JACC.2013;61:1713-23.
23. Kuck KH, Brugada J, Fu¨ rnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albeneque JP, Tondo C, for the FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374:2235–2245.