Assessment of Safety and Effectiveness in Treatment Management of Atrial Fibrillation with the BWI IRE Ablation System

AdmIRE IDE # G220034

PROTOCOL # BWI201910

Version 4.0

June 13, 2023

Sponsor: **BIOSENSE WEBSTER, INC.**
31 Technology Drive
Suite 200
Irvine, CA 92618
USA

1. Table of Contents

CCI [redacted]

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2. List of Tables and Figures

3. Responsible Parties Involved in the Study

SPONSOR:
Biosense Webster, Inc.
part of the Johnson & Johnson family of companies
31 Technology Drive, Suite 200
Irvine, CA 92618
USA

The sponsor maintains a list of CRO(s) and Core Lab(s) and their contact information.

INVESTIGATORS:
The sponsor maintains a list of study Investigators and their contact information.

4. Protocol Agreement and Statement of Compliance (Principal Investigator)

Study Title: Assessment of Safety and Effectiveness in Treatment Management of Atrial Fibrillation with the BWI IRE Ablation System

Study #: BWI201910

Principal Investigator:

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

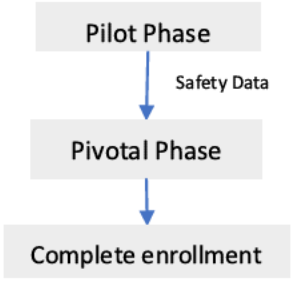
I will fulfill the requirements of my Institutional Review Board (IRB), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments and will accept respective revisions or amendments provided by the Sponsor.

_____	_____
Principal Investigator Name and Title [Print]	**Date**
_____	_____
Principal Investigator [Signature]	**Site ID**

5. Protocol Synopsis

Full Title & Protocol Number	Assessment of Safety and Effectiveness in Treatment Management of Atrial Fibrillation with the BWI IRE Ablation System
Short Title	AdmIRE
IDE number	G220034
Sponsor	Biosense Webster, Inc.
Indication	Drug refractory paroxysmal atrial fibrillation
Study Article Description	Biosense Webster IRE Ablation system consists of TRUPULSE™ Generator and VARIPULSE™ Catheter for cardiac electrophysiological mapping and ablation.
Premarket or Postmarket	Premarket
Study Design	Prospective, non-randomized, multi-center, clinical evaluation of the Biosense Webster BWI IRE Ablation system to demonstrate safety and long-term effectiveness comparing to corresponding performance goals. The study will include two sequential phases: • Pilot Phase • Pivotal Phase **Pilot Phase**: Acute safety data with at least 30 days of follow-up will be assessed . **Pivotal Phase**: The pivotal phase will enroll subjects in the roll-in and main phase. After the study ablation procedure, subjects will enter a 3-month blanking period (Day 0-90) followed by a 9-month evaluation period (Days 91-365). 
Sample Size	**Pilot Phase**: 20 evaluable subjects will be enrolled in the pilot phase. **Pivotal Phase**: Maximum of 408 subjects including:

	○ Roll-in cases: 1-2 cases per operating physician (with 1-2 physicians expected per site, and a maximum of 40 US sites, no more than 160 subjects will be included in the roll-in phase) ○ Main phase: 248 (225 evaluable PAF subjects plus 10% attrition)
Study Population	Subjects undergoing electrophysiology mapping and pulsed field ablation (PFA) for treatment of Antiarrhythmic Drug (AAD) refractory symptomatic paroxysmal AF.
Geographic areas to be included	Up to 40 sites in the US
Anticipated Study Duration	Total duration: Approximately 12 months of enrollment + 12 M of follow-up
Procedure(s) description	Ablation strategy: Subjects will arrive at the electrophysiology (EP) laboratory for their ablation procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator). The AF Ablation procedure will follow the below sequence: • Anatomical mapping of the LA • PVI using the study catheter • Confirmation of PV isolation in all targeted PVs by documented entrance block with adenosine/isoproterenol challenge • If necessary, treatment of acute reconnections or visual gaps with additional applications of PFA energy • If additional applications are applied, reconfirm PV isolation by documented entrance block of all targeted PVs • Prophylactic ablation of empirical sites is not allowed. • The ablation procedure is considered complete when confirmation of entrance block is confirmed and documented. In this study protocol, BWI IRE ablation system is used as the primary mode for achieving PVI. All subjects will undergo PV ablation with the VARIPULSE™ Catheter until PVI is achieved and isolation confirmed via documented entrance block. If PVI is not achieved with initial PFA applications, review remaining electrical signals and re-apply PFA energy with the corresponding electrodes using the VARIPULSE™ Catheter. A right atrial CTI linear ablation is allowed only in cases with documented typical atrial flutter either prior to or during the procedure. A commercially approved BWI RF catheter and compatible commercially available RF generator should be used.

<table>
<tr><td>Primary Objective</td><td>The primary objective of this clinical investigation is to demonstrate the safety and 12-month effectiveness of the VARIPULSE™ Catheter when used in conjunction with the TRUPULSE™ Generator for pulmonary vein isolation (PVI) in the treatment of subjects with symptomatic paroxysmal atrial fibrillation (PAF).
To demonstrate safety based on the incidence of subjects with early onset (within 7 days of ablation procedure) of primary adverse events.
To demonstrate 12-month effectiveness based on the proportion of subjects with freedom from documented atrial fibrillation, atrial tachycardia or atrial flutter (AF/AT/AFL) (hereinafter collectively referred to as “atrial tachyarrhythmias”) episodes during the effectiveness evaluation period (Day 91-365).</td></tr>
<tr><td>Primary Endpoints & Follow-up Intervals</td><td>Primary Safety

The primary safety endpoint is the incidence of early onset PAEs (within seven (7) days of an ablation procedure which uses the VARIPULSE™ Catheter and TRUPULSE™ Generator per protocol, including the initial and repeat procedures). PAEs include the following AEs:

<table>
<tr><td>Atrio-Esophageal Fistula*</td><td>Phrenic Nerve Paralysis (permanent)+</td></tr>
<tr><td>Cardiac Tamponade**,***/perforation**</td><td>Pulmonary Vein Stenosis++</td></tr>
<tr><td>Device or procedure related death+++</td><td>Stroke/CVA+,++</td></tr>
<tr><td>Major Vascular Access Complication/Bleeding</td><td>Thromboembolism</td></tr>
<tr><td>Myocardial Infarction</td><td>Transient Ischemic Attack (TIA)</td></tr>
<tr><td>Pericarditis</td><td>Pulmonary Edema (Respiratory Insufficiency)</td></tr>
<tr><td>Heart Block</td><td>Vagal Nerve Injury/ Gastroparesis</td></tr>
</table>
*Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.
**Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE
*** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.
+ Absent phrenic nerve function as assessed by a sniff test. Refer to Table 14.2.1.1 for permanent phrenic nerve paralysis definition.
++ Pulmonary Vein Stenosis occurring anytime during the 12-month follow up period will be considered a PAE.
+ Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported as a stroke
++ Modified Rankin score assessments should be made by certified individuals.
+++Device or procedure-related death anytime during or after the ablation procedure</td></tr>
</table>

	Primary effectiveness:
	Freedom from documented (symptomatic and asymptomatic) atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) episodes based on electrocardiographic data (≥30 seconds on ECG or sponsor provided TTM or Holter device) during the effectiveness evaluation period (Day 91-Day 365) and freedom from the following failure modes:
	• Acute procedural failure, including:
	  • Failure to confirm entrance block in all pulmonary veins (except those that are silent and/or cannot be cannulated post-procedure) at the end of the procedure
	• Repeat ablation failure, including:
	  • More than 1 repeat ablation procedures for AF/AT/ AFL (of unknown origin[+]) during the 3-Month Blanking Period (Day 0-90 post index procedure).
	  • Any repeat ablation procedure for AF/AT/ AFL (of unknown origin[+]) during the evaluation period.
	• Non-study catheter failure, including:
	  • use of a non-study catheter (NSC) to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) and/or to ablate left atrial non-PV AF targets during the index procedure
	  • use of a non-study catheter to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) during repeat procedure in the blanking period.
	• AAD failure:
	  • Taking a new AAD (Class I & III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) or taking a previously failed Class I/III AAD at a greater than the highest ineffective historical dose for AF/AFL/AT <u>past the 3-month follow-up visit window (i.e., from day 105-365 post index procedure)</u>
	• Continuous AF/AT/AFL of unknown origin[+] on a standard 12-lead ECG during the effectiveness evaluation period.
	• Any DC cardioversion procedure during the evaluation period for documented atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) recurrences ascertained through protocol specified arrhythmia monitoring methods(12-lead ECG, TTM and Holter).
	[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead electrocardiogram (ECG) and entrainment maneuvers in an EP study

Secondary Endpoints & Follow-up Intervals	Hypothesis-driven secondary endpoints: • QOL Improvement:
Additional Endpoints	CCI [redacted]

	CCI [redacted]
Inclusion Criteria	from enrollment, b. At least one (1) AF episode electrocardiographically documented within 12 months prior to enrollment. Electrocardiographic documentation may include, but is not limited to ECG;

	Transtelephonic monitoring (TTM), Holter monitor or telemetry strip, and c. A physician's note indicating recurrent self-terminating AF within 7 days. 2. Failed at least one (1) AAD (Class I or Class III) as evidenced by recurrent symptomatic AF, intolerable side effects to the AAD, or contraindication to the AAD 3. Age 18-75 years 4. Willing and capable of providing consent 5. Able and willing to comply with all pre-, post- and follow-up testing and requirements.
Exclusion Criteria	1. Previously diagnosed with persistent AF (> 7 days in duration) 2. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., untreated documented obstructive sleep apnea and acute alcohol toxicity). 3. Previous surgical or catheter ablation for AF 4. Patients known to require ablation outside the PV region (e.g., atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia and Wolff-Parkinson-White). 5. Documented severe dilatation of the LA (LAD >50mm) antero-posterior diameter on imaging within 6 months prior to enrollment. 6. Documented LA thrombus by imaging within 48 hours of the procedure. 7. Documented severely compromised LVEF (LVEF <40%) by imaging within 6 months prior to enrollment 8. Uncontrolled heart failure or New York Heart Association (NYHA) Class III or IV 9. History of blood clotting, bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran), 10. Documented thromboembolic event (including TIA) within the past 12 months 11. Previous PCI/MI within the past 2 months 12. Coronary Artery Bypass Grafting (CABG) surgery within the past 6 months (180 days) 13. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, valve repair or replacement and presence of a prosthetic valve). 14. Unstable angina within 6 months 15. Anticipated cardiac transplantation, cardiac surgery, or other major surgery within the next 12 months. 16. Significant pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms.

	17. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study 18. Prior diagnosis of pulmonary vein stenosis 19. Pre-existing hemi diaphragmatic paralysis 20. Acute illness, active systemic infection, or sepsis 21. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 22. Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm^2) 23. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the IRE energy field. 24. Presence of a condition that precludes vascular access (such as IVC filter) 25. Current enrollment in an investigational study evaluating another device or drug. 26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child-bearing age and plan on becoming pregnant during the course of the clinical investigation. 27. Life expectancy less than 12 months 28. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions for Use (IFU).
Statistical Analysis	CCI [redacted]
Interim Analysis	
Determination if DSMB/DMC/CEC required	

Time and Events Schedule:

	Pre-Procedure	Ablation/ Discharge		Phone/ Virtual	Follow-Up Visits				
	Screening / Baseline	Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	1	2	3	4	5	6	7	8	90
Informed consent[1]	X								
Inc & Excl Criteria	X								
Demographics	X								
Vital Signs	X								
Physical Exam including standardized neurological exam	X		X		X	X	X	X	X
Med History[2]	X			X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Hospitalization/ CV history	X								
AF History	X								
ECG	X[3]		X			X	X	X	X[3]
Adverse Events[4,5]	X	X	X	X	X	X	X	X	X
CHA_2DS_2-VASc and $CHADS_2$ Score	X								
NYHA Scale	X								
QOL Assessment[6]	X					X	X	X	
Pregnancy Test[7]	X								
LA size and LVEF imaging	X[8]								
LA Thrombus Imaging		X[9]							
Ablation Assessments		X							
Device Deficiency		X							
TTE		X[10]							
Concomitant Medications[11]	X	X	X	X	X	X	X	X	X
Repeat Ablation					X	X	X	X	X
AF/AT/AFL recurrence			X	X	X	X	X	X	X
TTM [12]					(X)	X	X	X	
24 Hr Holter							X	X	

	Pre-Procedure	Ablation/ Discharge		Phone/ Virtual	Follow-Up Visits				
	Screening / Baseline	Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	1	2	3	4	5	6	7	8	90
Completion/ discontinuation form[13]		X	X	X	X	X	X	X	

1 Initial ablation procedure should be done within 90 days of consent.
2 Collected to confirm no changes in medical history since last visit
3 Data from 12-lead ECG recordings will be collected, if available.
4 AEs collected once consent has been signed. Collected to confirm no changes in health status since last visit. Refer to Table 14.2.1.1 for any additional non-SOC diagnostics required to confirm PAEs.
5 If AE results in hospitalization, data should be collected.
6 Quality of life tools (AFEQT and CCS-SAF).
7 Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.
8 Imaging should be done within 6 months prior to enrollment.
9 Subjects must undergo imaging for the presence of LA thrombus within 48 hours of the ablation procedure.
10 All subjects will undergo TTE prior to discharge to evaluate pericardial effusion
11 Concomitant medications: only cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.).
12 Collected weekly starting from 1-month visit through end of month 5 post procedure, (required during the evaluation period, day 91 post procedure) and then required monthly from month 6 post procedure through the end of the evaluation period and during all symptomatic cardiac episodes from the time they receive the TTM device.
13 12-month visit/last completed visit or last data collection

6. Background Information and Scientific Rationale

6.1 Background

Catheter ablation is the treatment of choice for patients with cardiac arrhythmias who are refractory to anti-arrhythmic drugs [1]. New evidence suggested that catheter ablation was more beneficial than medical therapy in patients with untreated or under-treated atrial fibrillations [2]. Catheter ablation therapy significantly reduced AF recurrences and cardiovascular-related hospitalizations and significantly improved the quality of life [2, 3]. Most of the catheter ablation systems are thermal energy-based and use either heat or cold energy to destroy arrhythmogenic tissues. However, creation of tissue lesions by thermal energy ablation is time consuming and requires energy titration. The ablation has been connected with high rate of arrhythmia recurrences due to incomplete lesion creation. It is also associated with severe complications such as pulmonary vein (PV) stenosis, phrenic nerve damage, coronary artery damage, atrioesophageal fistula, steam pop and ensuing cardiac perforation and pericardial tamponade [1, 4, 5].

In the past decades, extensive research into alternative energy forms for ablation has been conducted to improve ablation efficiencies and reduce ablation-related complications. One of the new technologies for lesion creation is called irreversible electroporation (IRE). Electroporation is a process in which an electric field is applied to the cell/tissue for a short period of time that results in pore formation in the cell membrane and a subsequent increase in cell permeability [6]. The electric field strength and duration could cause reversible or irreversible permeabilizations[7]. At low electric field strength and a short duration, the cell membrane forms nanosized pores, allowing small or medium sized molecules, such as drug and DNA, flow across the lipid bilayer. The pore formation is transient and reversible. The affected cells are able to survive from this reversible electroporation. At medium electric field strengths, the density of pore formation in the membrane increases to a certain level such that the process becomes irreversible. Free flows of water and ions in and out of the cell membrane result in the loss of cellular homeostasis, ultimately triggering the apoptosis and cell death. This irreversible aspect of the process is thus called “irreversible electroporation” or IRE [1, 6]. Finally, at high electric field strengths, the cell membrane quickly undergoes fragmentation resulting in necrotic cell death [6]. Such high levels of electric field strengths are not suitable for therapeutic applications and should be avoided.

The PFA system generally consists of electric field generator and electric current applicators. The electric field required for IRE could be delivered by applying a high voltage or direct current (DC) across electrodes within or in contact with cardiac tissues [6]. Different kinds of electric currents, such as DC, alternate current (AC), pulsed DC, or a combination of these were used to generate the electric field for IRE in preclinical and clinical studies [8]. Pulsed DC was the most commonly used energy source in preclinical and clinical studies [9, 10]. Early studies found that the strength of the electric field delivered by pulsed DC is dictated by pulse shape, pulse duration, pulse height, pulse polarity, pulse interval, number of pulses per application or pulse train, number of pulse trains delivered, and interval between pulse train deliveries [6, 7, 11]. In custom built generators, many of

those parameters are adjustable. Therefore, optimal electric field strengths and parameters could be determined and controlled.

The use of IRE technology advanced rapidly in the field of oncology in 1990s.

The success of IRE technology in the treatment of tumors revitalized the interest of its application in the treatment of cardiac arrhythmias recently [12]. Many preclinical studies as well as a clinical study were conducted since 2007 to investigate efficacy, safety, and underline histopathological mechanisms. It was demonstrated that seemed to be tissue specific by sparing the coronary arteries, the phrenic nerve, and the esophagus while producing lesions to achieve pulmonary vein isolation.

6.2 Advantage of IRE Technology

The IRE technology uses non-thermal energy for lesion creation, which is different from the other technologies used for cardiac ablation. During IRE ablation, application of electric fields in the cardiac tissue causes irreversible changes in the permeabilization of the cell membrane, leading to cell apoptosis and death [6].

Early data shows PFA prevents collateral damage to non-cardiac structures, including the prevention of pulmonary vein stenosis, phrenic nerve damage and esophageal injuries. This safety benefit would allow the physician to apply energy effectively in areas where the risks of collateral damage associated with thermal ablation modalities imposes workflow constraints and complexities while frequently tempering therapeutic energy delivery.

The BWI IRE Ablation System provides a novel approach for the treatment of cardiac arrythmias by using pulsed electrical field (PEF) energy to produce targeted intracardiac lesions and achieve the intended therapeutic effect. While currently approved systems rely on thermal energy to destroy (ablate) aberrant cardiac tissue, the BWI technology ablates targeted cardiac tissue by means of irreversible electroporation (IRE) which results from inducing cell membrane permeability and subsequent ablation by application of ultrashort electrical pulses. Commonly considered tissue selective, this technology, referred to as pulsed field ablation (PFA), expands the therapeutic window for cardiac ablation by mitigating the risks of thermal injury and serious adverse events associated with other catheter-based approaches.

In a bipolar PFA energy delivery modality, multiple, brief electrical pulses are delivered within fractions of a second across the electrodes without the use of an external patch (which is necessary when the PFA is uni-polar). Each pulse is comprised of a waveform which has a predefined amplitude, pulse width, and duration. When applied to myocardial cell membranes, these pulses induce nanoscale pores in the cell membrane, increasing permeability with leakage of cell contents. This phenomenon, also referred to as irreversible electroporation, subsequently results in either immediate necrosis or delayed apoptotic cell death.[1,3-7]

The earliest publicly available studies of PFA on animal cardiac myocytes showed the feasibility and safety in porcine models using PFA, demonstrating the myocardial selectivity and non-thermal

effects on the esophagus, phrenic nerve and in the pulmonary vein. Since then, refinements of various pulse sequences have helped advance the technology into the clinical arena where reports of durable lesion creation are reinforcing expectations of positive long-term effectiveness outcomes.[12]

6.3 Previous Experience with Biosense Webster IRE Ablation System

Biosense Webster, Inc (BWI) has developed an IRE ablation system consisting of a TRUPULSE™

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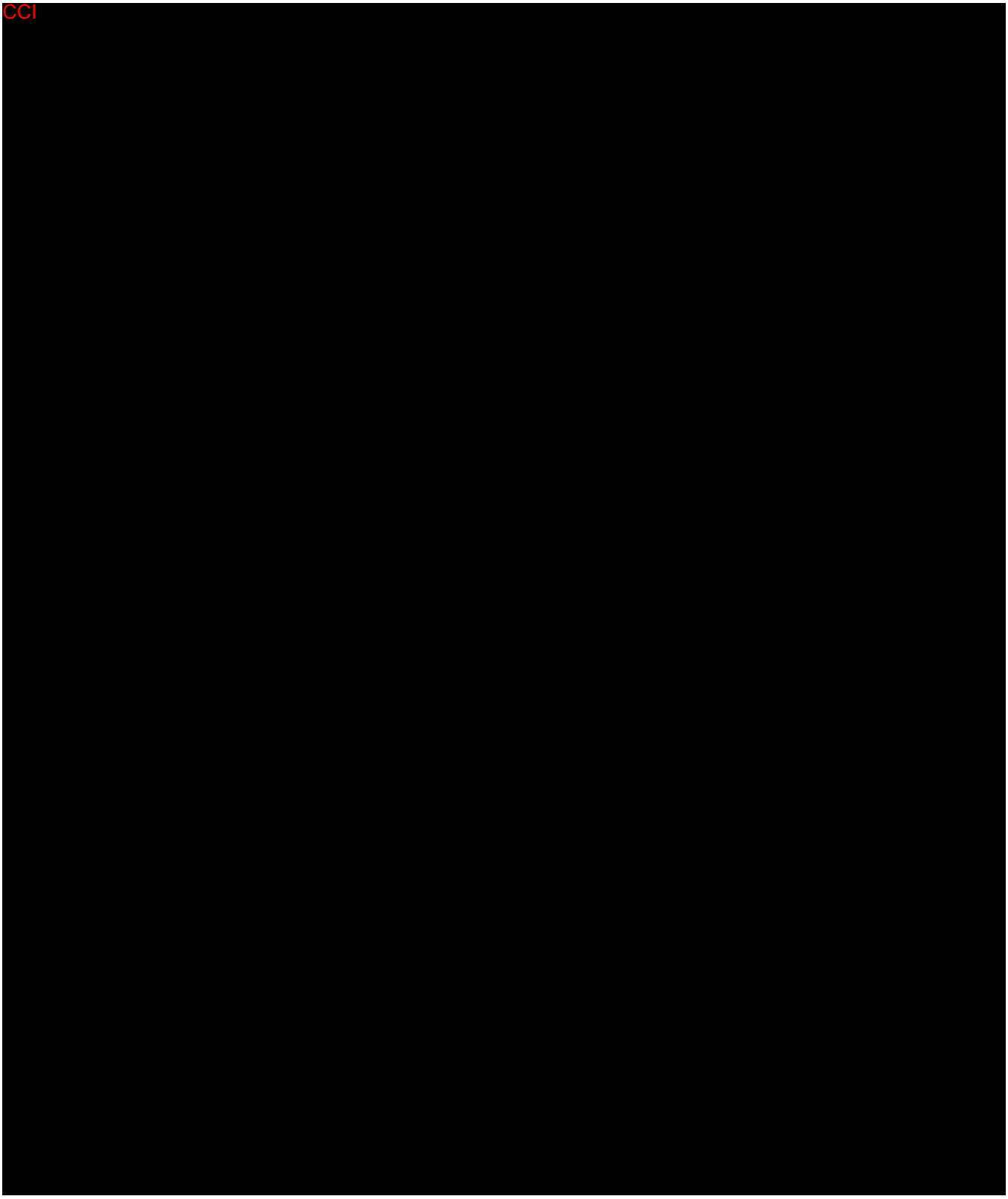
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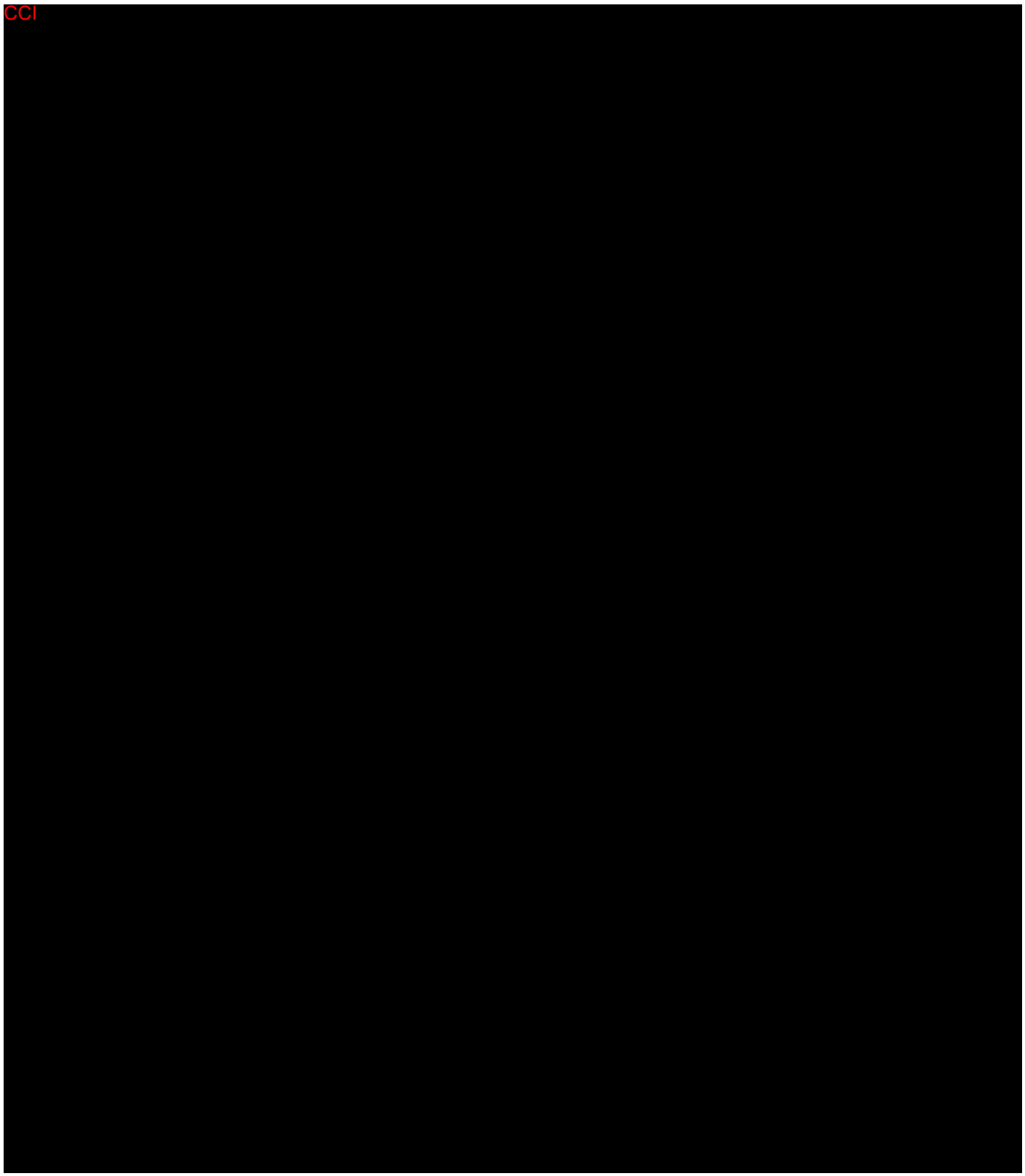
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The types of procedural risks posed by the BWI IRE Ablation system are expected to be comparable to the known anticipated risks of conventional electrophysiology catheterization procedures. PFA

technology is expected to reduce the incidence of the most severe risks associated with traditional electrophysiology catherization procedures. There are also some risks that can occur with traditional ablation therapies, that may occur more frequently with PFA energy during ablation therapy, such as harms associated with arcing, acute pain from muscle contraction, and arrythmia induced by vagal responses.

6.4.2 Risks Associated with Catheter Ablations

Certain AEs associated with thermal energy-based percutaneous electrophysiological procedures could also occur during IRE ablations.

Cardiac perforation/ Pericardial effusion/ cardiac tamponade: Cardiac perforation may result from catheter manipulation (risk is <1% in RF ablation catheter). Cardiac perforation may result in pericardial effusion or cardiac tamponade which requires percutaneous pericardial drainage or surgical repair [5].

Pulmonary vein stenosis: Pulmonary vein stenosis (PVS) is a well-known complication of thermal catheter ablation of atrial fibrillation. In RF procedures, the risk of PV stenosis is small (<4%) and can be prevented by delivering energy outside of the pulmonary vein ostium [5]. The risk of pulmonary stenosis associated with a pulsed field energy ablation procedure is expected to be unlikely and to date has not been reported following pulsed field applications [13, 14].

Atrio-Esophageal Fistula (AEF)/Esophageal injury: AEF is a rare but catastrophic complication of AF ablation that can occur due to the anatomical proximity of the esophagus to the posterior wall of the LA and that is associated with a high mortality rate [15]. In patients, the application of traditional thermal energies along the posterior LA can result in thermal injury to the esophagus and the formation of an AEF [5]. In contrast, due to the extremely limited thermal effects of pulsed field ablation, the risk of AEF is expected to be extremely low and has not been reported following PFA to date in the literature [16]. The number of preclinical and clinical studies have demonstrated that serious esophageal injury is unlikely with PFA. However, the data on impact of extreme overapplication of pulse field energy on the esophagus has not reported to date.

Phrenic nerve paralysis: Currently, permanent phrenic paralysis has been reported in less than 0.4% of traditional PV treatment procedures. Injury to the Phrenic Nerve (PN) is unlikely with the pulsed field energy provided. A limited number of preclinical and clinical studies have suggested that the risk of phrenic nerve paralysis is unlikely following PFA. However, irritation of the phrenic nerve that resolves acutely has been noted in the literature [17].

Death: Death was an uncommon complication associated with catheter ablation techniques. The most frequent causes of death were cardiac tamponade, stroke, atrioesophageal fistula and massive pneumonia [18]. The overall incidence of death in AF ablation has been reported to be <0.1% to 0.4% [5]. Reduced incidence of atrioesophageal fistula and coronary artery damage with IRE technology further reduces the incidence of death.

Cerebral ischemic lesions: According to HRS guidelines, 2017, the incidence of Asymptomatic Cerebral Embolism (ACE) varies from 2%- 15% as a complication to AF ablation [5]. As pulsed field ablation is a new energy modality for treating Atrial Fibrillation, there is limited data on the potential for incidence of cerebral ischemic lesions. An ACE is defined as an occlusion of a blood vessel in the brain due to an embolus that does not result in any acute clinical symptoms and is therefore ‘silent’. Emboli can result

from a thrombus, gas, air, tissue or fat. Source of micro-emboli include thrombi, which can develop on sheaths, materials, air introduction through sheath or during catheter exchange. Additionally, the risk of ACE as a result of the hazard of microbubble formation in pulse field ablation leads has not been determined [19]

Thromboembolic events: The mean incidence of thromboembolism associated with AF ablation was reported by Cappato et al in 2010 to be between 1% and 2%[20]. Thrombus generated during the ablation procedure may pose a serious and even life-threatening risk to the patient. Thrombus could form during IRE ablations due to insufficient level of anti-coagulants or lack of irrigation. Embolization of thrombus could produce stroke, Myocardial Infarction (MI), or other ischemic injury.

Pulmonary injury: Pulmonary injury, such as pneumothorax and pulmonary hemorrhage, is a rare but severe complication of PVI. Mechanical trauma from catheter manipulation is a possible mechanism for pulmonary hemorrhage. Pneumothorax might be caused by thermal injury during traditional RF injury [21]. To date, the literature has not reported any incidences of pulmonary injury due to pulsed field ablation.

Pericarditis: With any circular-based ablation, pericarditis can occur due to mechanical or thermal irritation of the myocardium. The 2017 HRS Consensus statement states it may occur anywhere between 0-50%. However, pericarditis tends to be usually transient and resolves without intervention [5].

Heart block: The application of pulse field energy close to the AV node or HIS bundle could damage or destroy the normal AV conduction system, producing complete heart block and requiring implantation of a permanent pacemaker.

Vascular access / bleeding complication: Vascular access complication, femoral arteriovenous fistula, hematoma, and pseudoaneurysm are commonly reported in procedures requiring femoral access. Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels occur in rare circumstances (risk <1%). These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ. Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion [5].

Gastric Hypomotility and Periesophageal Vagal Nerve Injury: Injury to the vagal anterior esophageal plexus can occur with traditional thermal energy such as RF energy is applied to the posterior wall of the LA, which can cause acute pyloric spasm and gastric hypomotility. Common symptoms include nausea, vomiting, bloating, and abdominal pain developing within a few hours to a few weeks after the ablation procedure[5]. Vagal nerve injury is unlikely with PFA ablation and has not been reported in published data to date.

Radiation exposure: Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%) [22-24].

Allergic Reaction: A patient could develop an allergic reaction to the local or systemic anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%) [25-29]. If an allergic reaction occurs, typical standard of care (SOC) should be applied.

Infection: Percutaneous procedures carry the risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%). This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents[5].

Arrythmia and Vagal response: vagal responses (VRs) such as bradycardia, sinus arrest, and atrioventricular block frequently occur, and are known to happen with both RF and PFA technologies [30-32]. Vagal responses may be associated with simultaneous modification of intrinsic cardiac autonomic nervous system expression. Extreme vagal response resulting in prolonged asystole should be treated using clinical standards of care. Additionally, cardiac arrythmia may be induced during an AF ablation procedure.

Pain: Pulse field ablations have been associated with muscular contraction in the literature[33]. These contractions can cause acute or post procedural patient discomfort. Patient comfort should be maintained through standards of care pain management.

Hypervolemia/Fluid Overload: The Circular IRE Catheter is an irrigated catheter. Excessive use of irrigation could cause hemodynamic imbalance. To prevent hypervolemia, ensure that the catheter is used per its instructions for use.

Cardiac perforation, Heart Block or valve rupture (resulted from barotrauma or arcing): The literature for early DC ablations indicates barotrauma has a broad term for resultant harm from electrical arcing [11, 34]. Biosense Webster has assessed the risks for patient injuries from arcing to include Cardiac perforation, Heart Block or valve rupture. The recent, available published data has not shown any evidence of barotrauma. Barotrauma has not been reported in published data. Nonetheless, to prevent such harms, the physician should use the catheter and generator per their intended directions for use.

Contraindications: Contraindications for catheter ablation of arrhythmia include active systemic infection, existing hemodynamic instability, bacteremia, coagulopathy, prosthetic valves, myxoma, intra-atrial or venous thrombosis, and pregnancy. Additional contraindications for PFA ablation include metal implants.

6.4.3 Risk Mitigation

Appropriate measures have been outlined in the study protocol to minimize the risk to subjects, while still providing the possible benefits of the treatment options to be studied. Although cardiac IRE ablation procedures pose potential risks, the criteria for subject selection, methods, personnel, facilities, and training that have been specified for this study are intended to minimize the risk to subjects undergoing this procedure.

Robust testing of the investigational devices at the component and the system level, within simulated clinical conditions, was successful with no adverse events identified.

The criteria for subject selection, methods, personnel, facilities, and training that are specified in this study are intended to minimize the risk to subjects undergoing this procedure.

Subjects will be screened carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to eliminate confounding co-morbidities that might interfere with study interpretation and exclude subjects with a medical history or condition that increases their risk of adverse events.

Subjects will be evaluated for the presence of left atrial thrombus prior to the procedure which is intended to decrease the potential for thromboembolic complications.

Participating investigators will be experienced and highly skilled in performing electrophysiology studies, intracardiac mapping and ablation of cardiac arrhythmias with other ablation catheters. Before this clinical study, investigators will undergo device training prior to performing study ablation procedures and in accordance with the physician training charter. Investigators will be trained on efficient maneuvering of IRE catheters and lesion creation on the sites similar to the target sites in human. Each site's Investigator will have satisfied the established training criteria. Procedures will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. The laboratory will contain sufficient resuscitative equipment and facilities to manage any potential complications. Immediate access to cardiac surgical facilities, as well as a qualified cardiovascular surgeon, will be available during the ablation procedure in the event that surgical intervention becomes necessary.

The risk of PNP will be minimized by monitoring the PN with pacing maneuvers before and during the ablation of the right sided PVs. Investigators are encouraged to ensure diaphragmatic capture prior to and post ablation when in the region of the RSPV.

Optimal anti-coagulation prior to procedure, using Heparin to achieve an activated clotting time (ACT) of 350 seconds, during procedure and anticoagulation therapy for 2 months post procedure, can substantially decrease the risk of thrombus formation. Continuous irrigation of the catheter per IFU should reduce the risk.

The risk of ACE will be minimized by implementing an anti-coagulation regimen procedure and during procedure to avoid thrombi/emboli during procedure. Investigators will be instructed to minimize catheter exchange during procedure to mitigate the risk of air introduction. A single transseptal technique is recommended, with administration of heparin bolus prior to transseptal puncture.

To prevent effusion and tamponade, the VARIPULSE™ Catheter should be used as instructed, including ensuring that the loop of the catheter is not turned in a counterclockwise manner while inside of the patient.

To prevent the risk of pulmonary injury, investigators will be instructed to follow the recommended workflow.

To reduce the incidence of heart block the investigators are instructed to follow the recommended workflow.

In accordance with the 2020 ESC AF Management Guidelines[35], all subjects should be maintained on systemic oral anticoagulation therapy for at least two months post-procedure. In addition, the study protocol requires subjects to be on uninterrupted anticoagulation prior to the procedure. After two months post-procedure, a decision regarding continuation of systemic anti-coagulation agents will be based on the subject's risk for thromboembolism.

Finally, safety data will be evaluated periodically by a Data Monitoring Committee (DMC) as described in the DMC Charter. A Clinical Events Committee (CEC) will be implemented to adjudicate the primary safety endpoint events. The CEC will operate as described in the CEC Charter.

6.4.3 Precautions

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the subject. The risk of serious complications is generally related to the severity of cardiac disease. The degree of risk of the electrophysiological and catheter ablation procedures versus the potential benefit of the treatment of a cardiac arrhythmia should be determined by a qualified physician. Cardiac catheterization and electrophysiological procedures should be performed by qualified and appropriately trained personnel in an electrophysiology laboratory. The laboratory should contain sufficient resuscitative equipment and facilities to manage most potential complications. Failure to observe the contraindications, warnings, and precautions in these instructions and the instruction for use (IFU) may result in procedural complications. Immediate risks from ablation treatment may include: cardiovascular injury or perforation with or without cardiac tamponade, pulmonary embolus, tricuspid regurgitation, myocardial infarction, bleeding at the catheter insertion site, sepsis, and death.

Contraindications for catheter ablation of arrhythmia include: existing hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy.

6.4.4 Known Potential Benefits

The treatment of AF by catheter ablation with pulmonary vein isolation (PVI) is considered as the cornerstone of treatment of AF[5]. Data published from many recent prospective multi-center clinical trials for ablation devices demonstrate that acute PVI is a reliable treatment in reducing long-term recurrence of PAF. The energy modality that has been most predominantly used for pulmonary vein isolation (PVI) has been radiofrequency (RF)[5]. RF ablation destroys cells through conductive and resistive tissue heating[36]. While highly efficacious, collateral damage and thermally induced injuries, such as esophageal fistula and PV stenosis, are rare but serious adverse events posed by the procedure[5].

Published animal and human studies demonstrate the potential for PFA to be a safe and efficacious way to deliver energy for pulmonary vein isolation via a non-thermal ablative modality [37, 38]. PFA has an additional benefit of being tissue selective, which reduces risk of collateral tissue injury. PFA energy can be applied selectively to cardiac cells, while preserving surrounding tissue [37].

The BWI IRE Ablation System provides a novel approach for the treatment of cardiac arrythmias by using pulsed electrical field (PEF) energy to produce targeted intracardiac lesions and achieve the intended therapeutic effect. The VARIPULSE™ catheter is intended to allow for the ablation of larger areas of

tissue compared to traditional single tip catheters. This allows for shorter operator learning curves, faster total procedure times by creating a circumferential contiguous lesion in the pulmonary vein, and also reduces the number of catheter exchanges.

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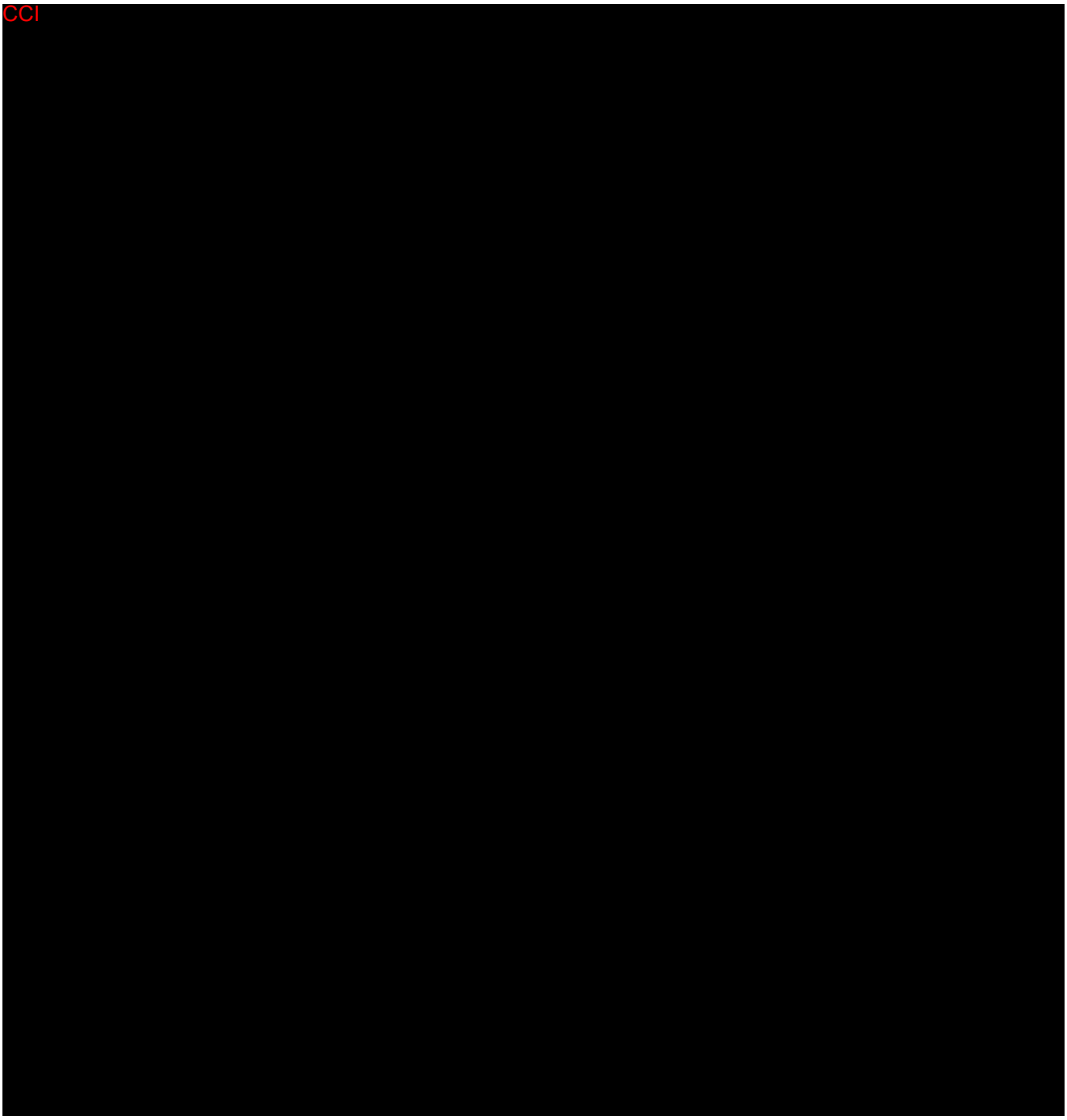

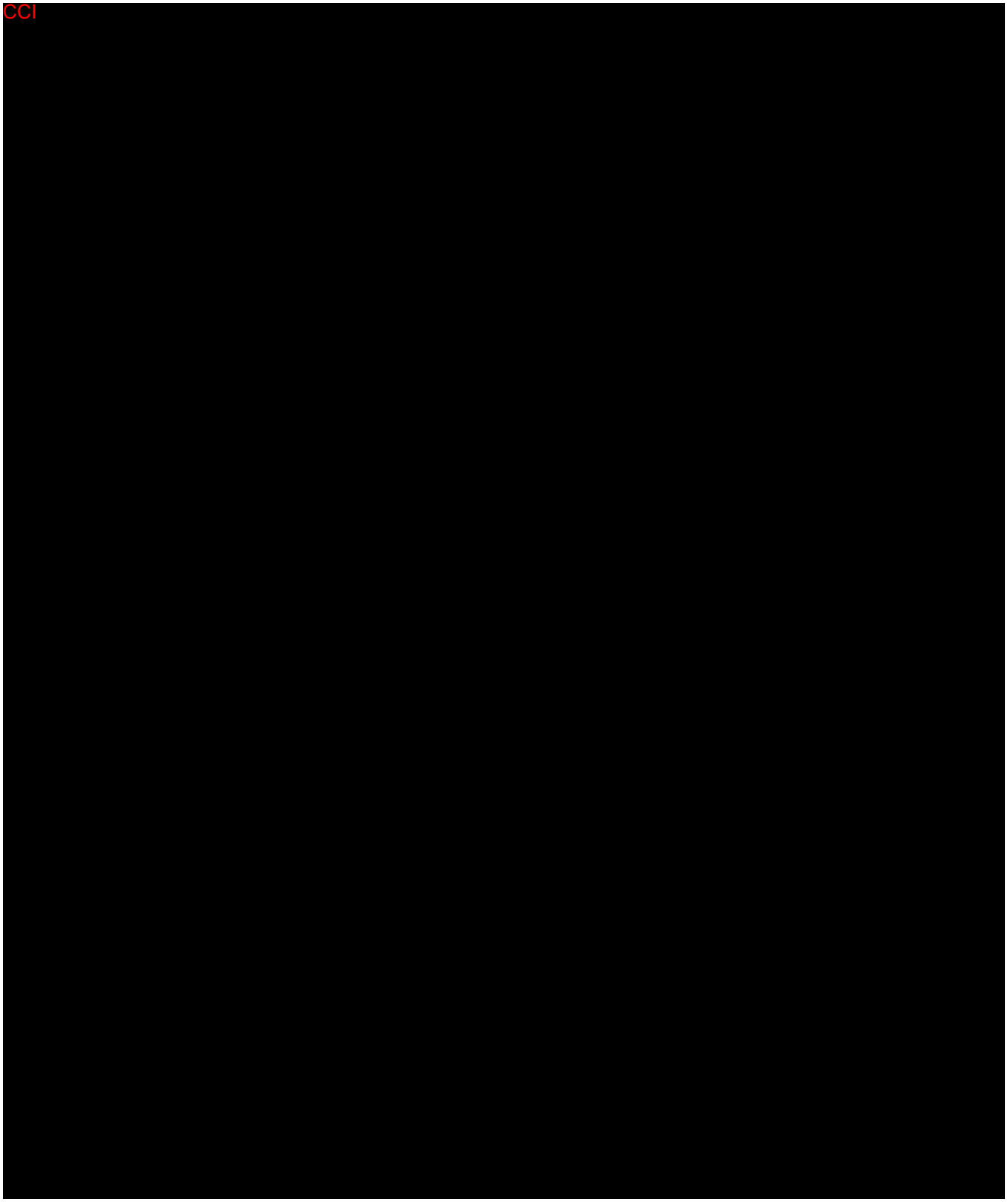
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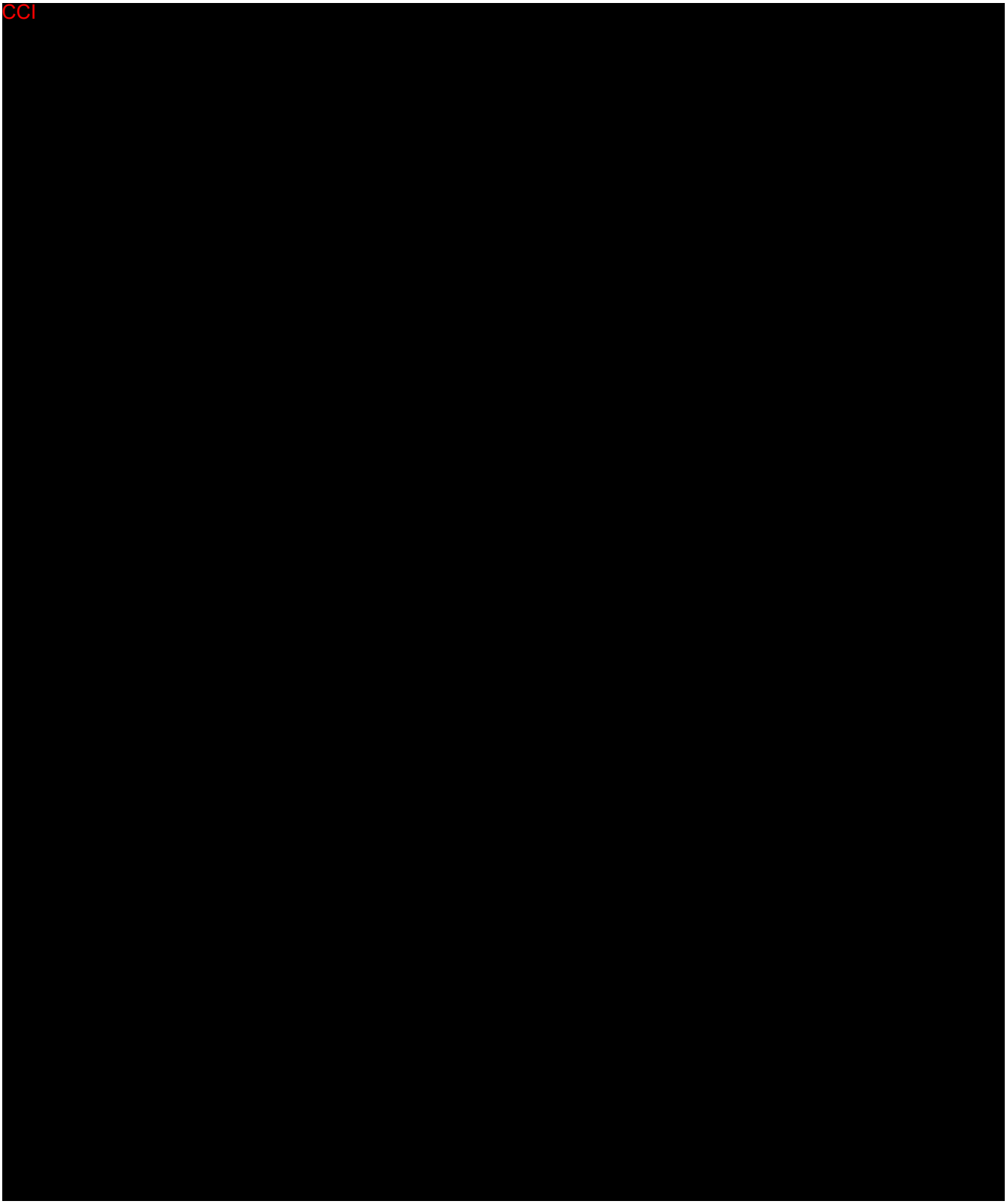
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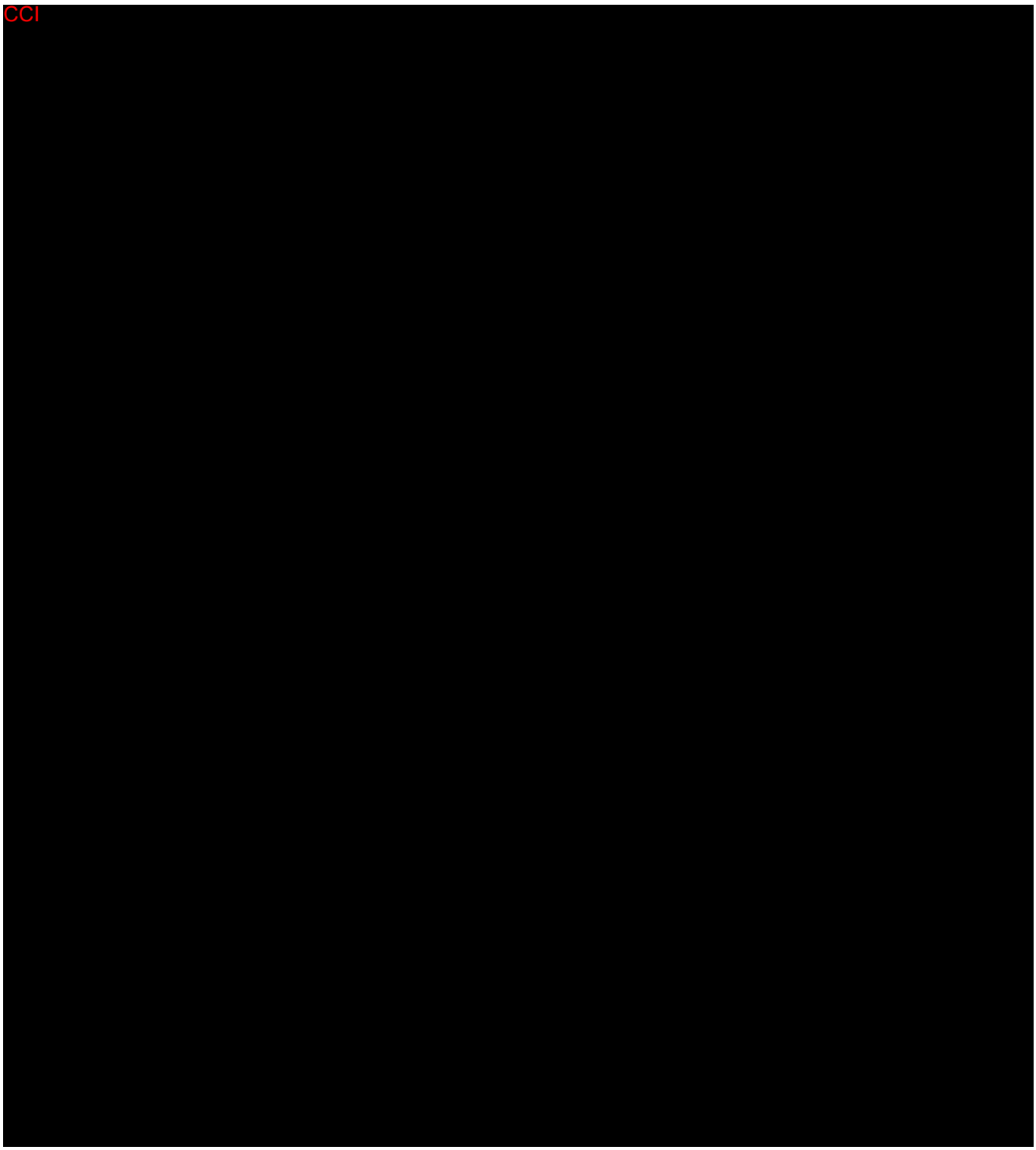

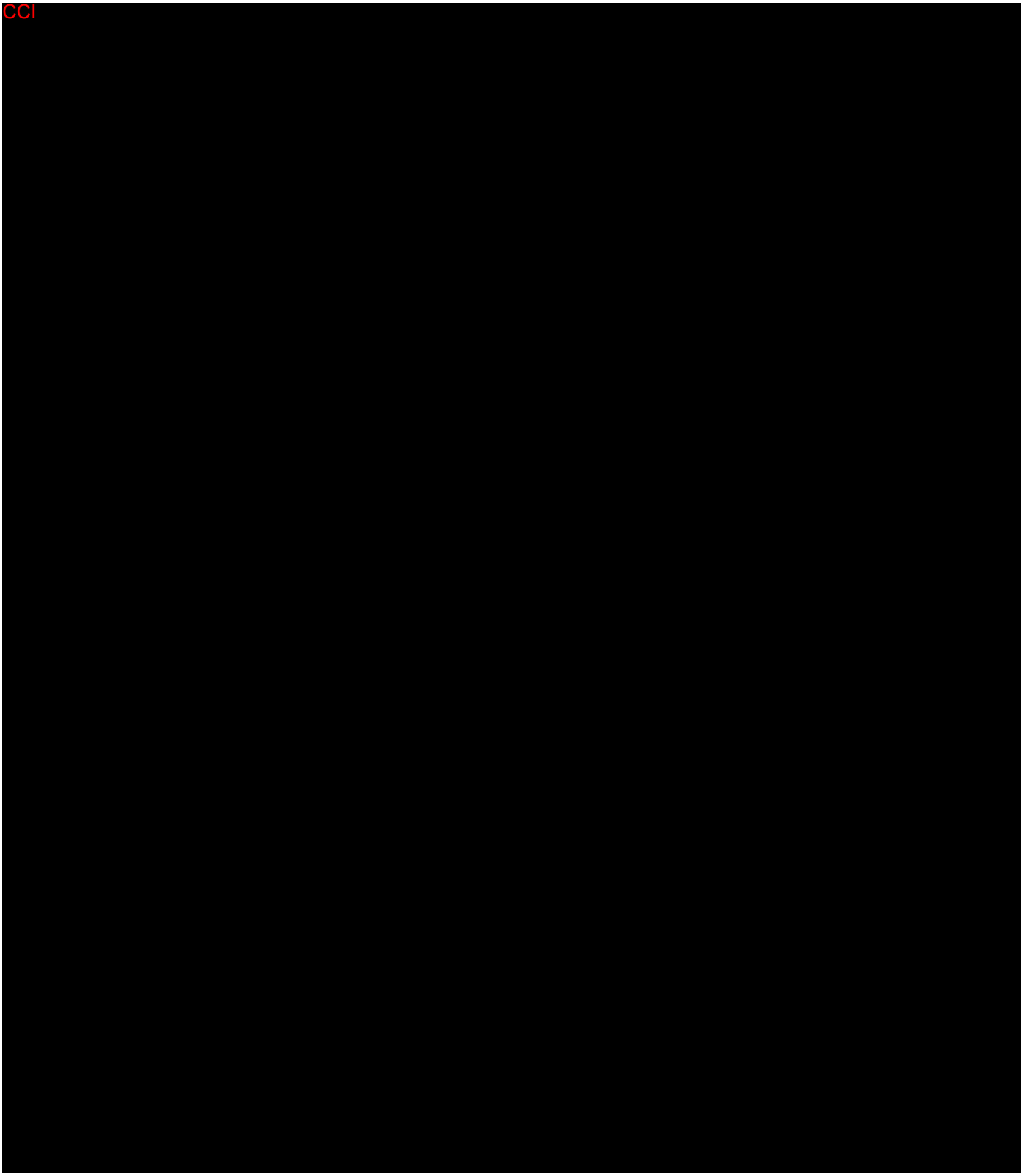
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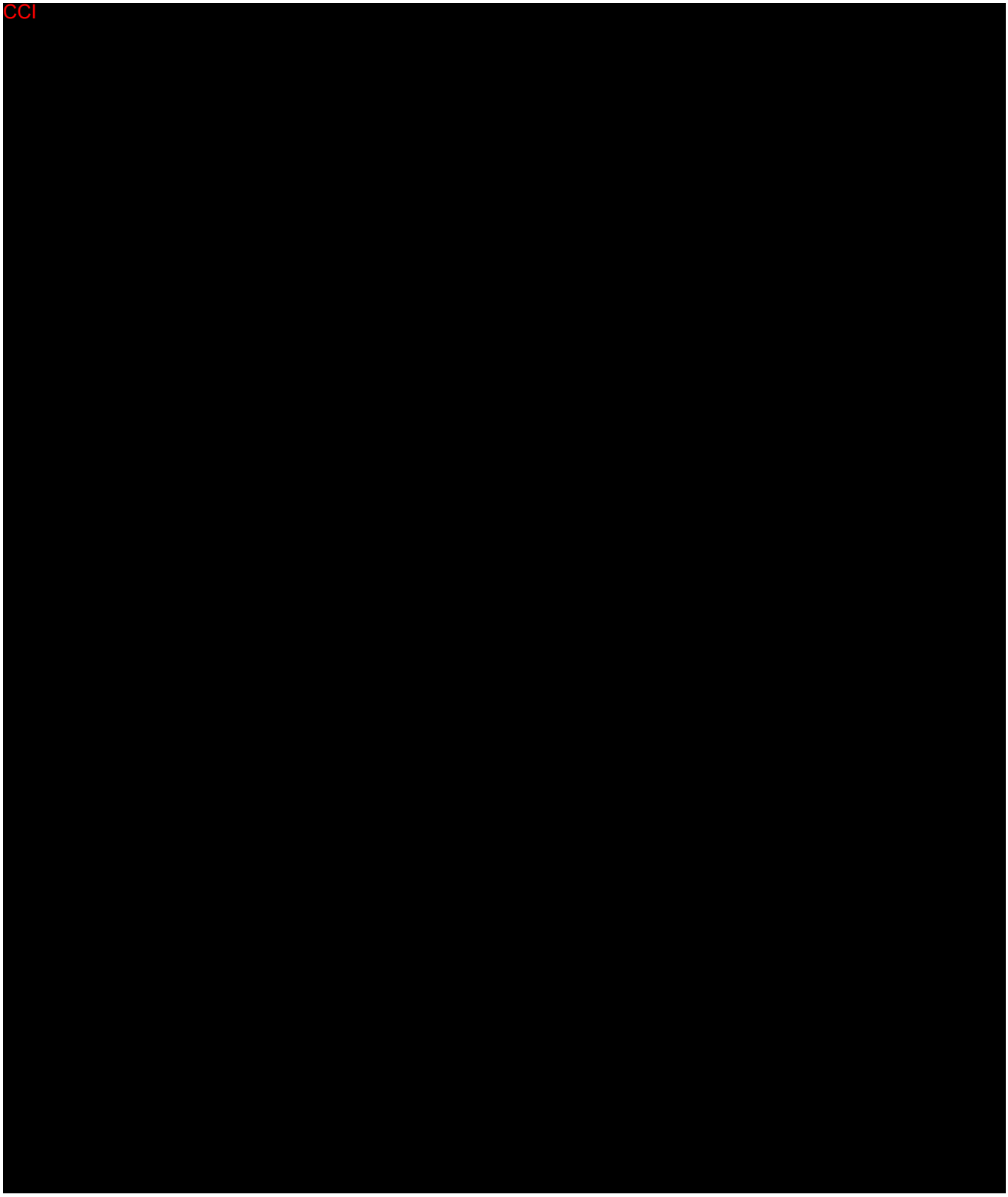
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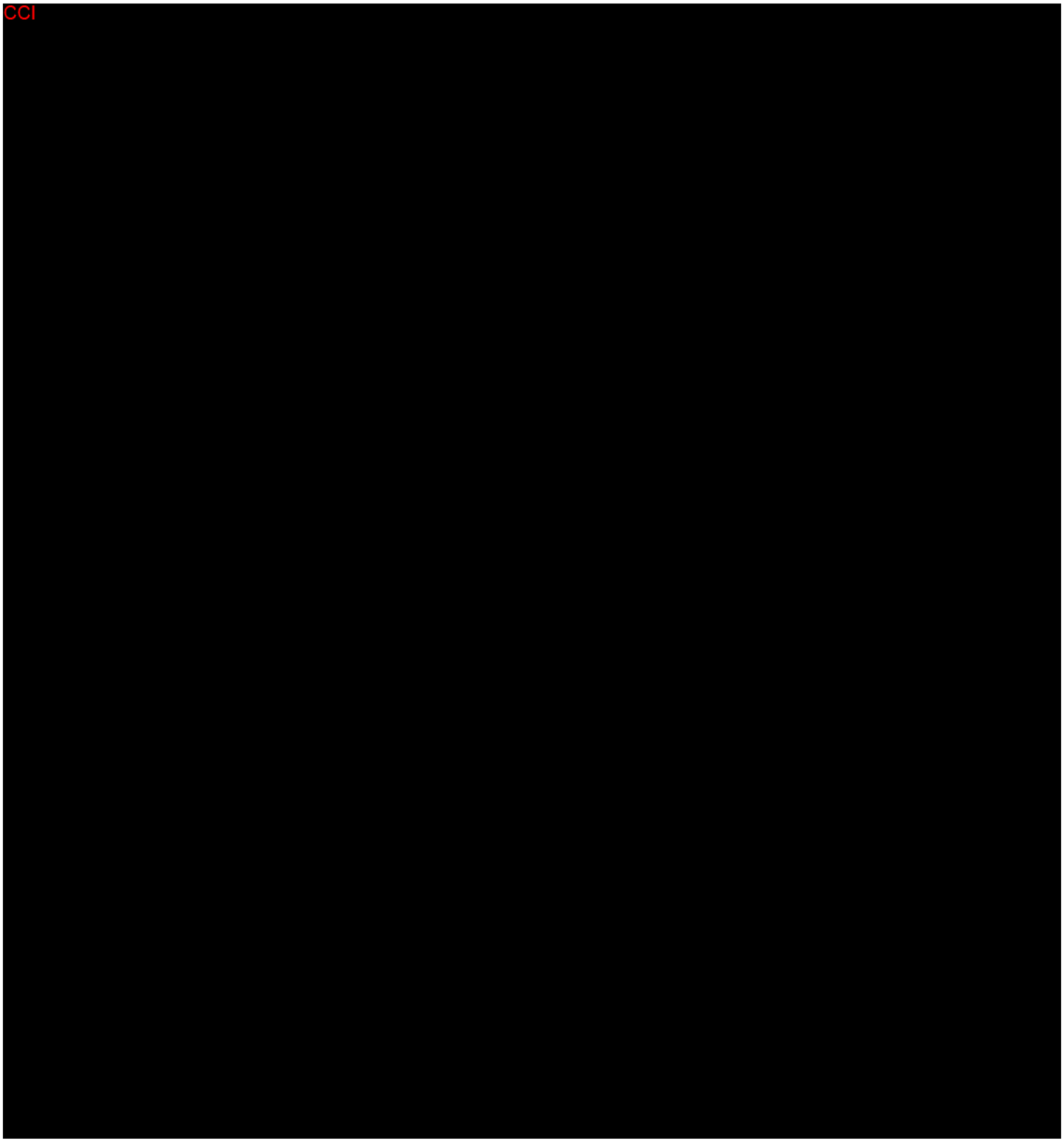

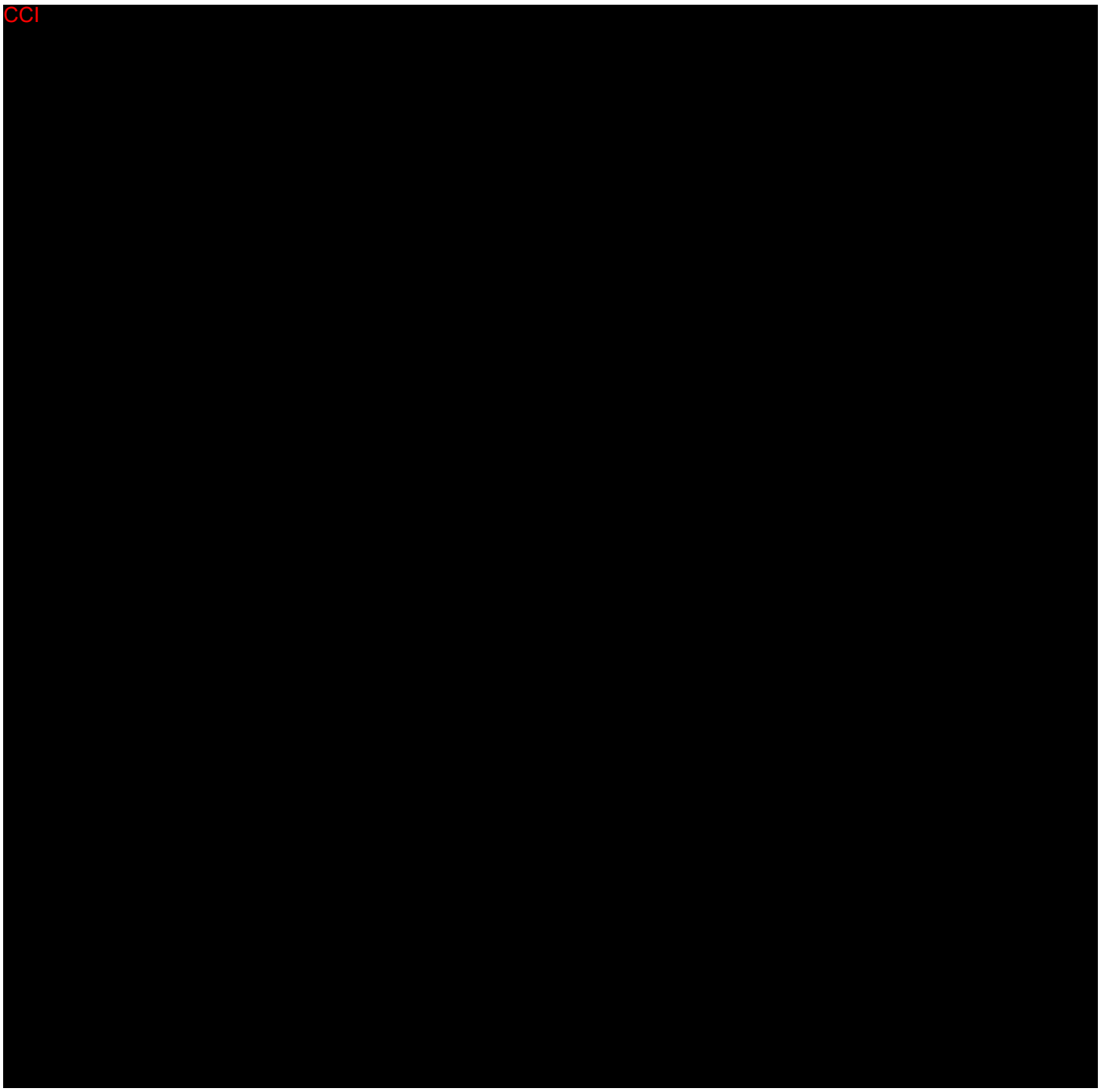
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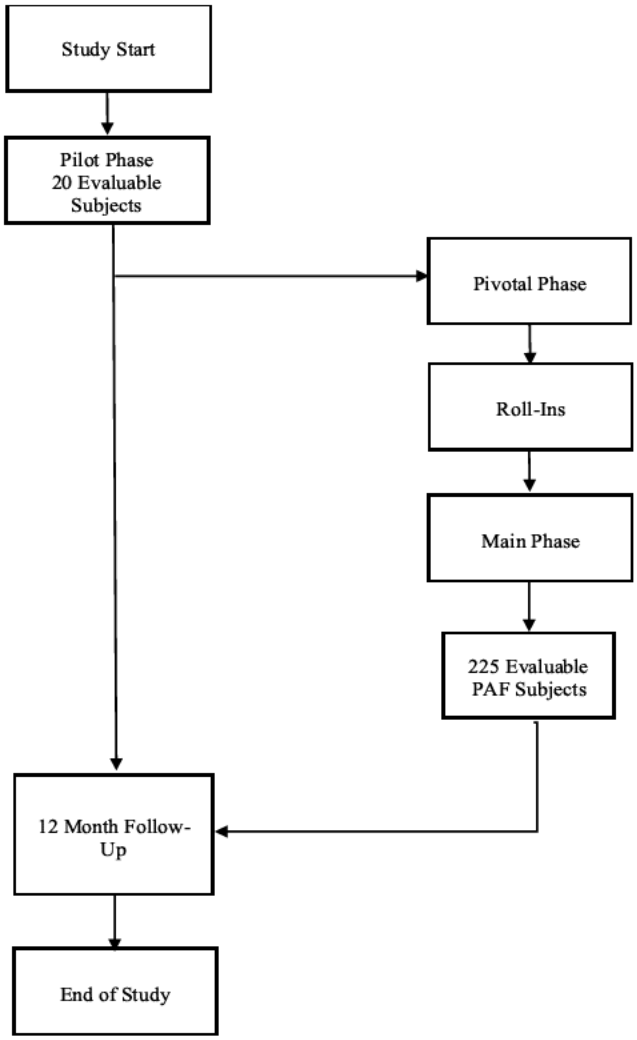

Figure 9.1.1: The schematic of study design

Patients who sign the Informed Consent Form (ICF) will be treated with the VARIPULSE™ Catheter and TRUPULSE™ Generator. Study subjects will be followed for 12 months after the study index procedure. Up to 40 sites in the United States will participate in this study.

The study consists of two sequential phases, a Pilot Phase and a Pivotal Phase.

9.1.1 Pilot Phase

The pilot phase will enroll a total of 20 evaluable PAF subjects.

9.1.2 Pivotal Phase

The pivotal phase will consist of the roll-in and main phase.

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The primary safety endpoint is the incidence of early onset PAEs (within seven (7) days of an ablation procedure which uses the VARIPULSE™ Catheter and TRUPULSE™ Generator per protocol, including the initial and repeat procedures). PAEs include the following AEs:

Atrio-Esophageal Fistula[*]	Phrenic Nerve Paralysis (permanent)[+]
Cardiac Tamponade[**,***]/perforation[**]	Pulmonary Vein Stenosis[++]
Device or procedure related death[+++]	Stroke/CVA[†,††]
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	Transient Ischemic Attack (TIA)
Pericarditis	Pulmonary Edema (Respiratory Insufficiency)
Heart Block	Vagal Nerve Injury/ Gastroparesis

*Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.

**Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE

*** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.

[+] Absent phrenic nerve function as assessed by a sniff test. Refer to Table 14.2.1.1 for permanent phrenic nerve paralysis definition.

[++] Pulmonary Vein Stenosis occurring anytime during the 12-month follow up period will be considered a PAE.
[+] Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported

[++]

CCI [redacted]

atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) episodes based on electrocardiographic data (≥30 seconds on ECG or sponsor provided TTM or Holter device) during the effectiveness evaluation period (Day 91-Day 365 post index procedure) and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to confirm entrance block in all pulmonary veins (except those that are silent and/or cannot be cannulated post-procedure) at the end of the procedure

  Note: Subjects who have the study catheter inserted but do not undergo ablation with PFA energy delivery via the study catheter due to IRE system related reasons will be considered as acute effectiveness failures; subjects who are discontinued due to non-IRE system related reasons (e.g., pump, other equipment or anatomy that precludes treatment with the VARIPULSE™ catheter or a commercially available catheter) will not be considered as acute effectiveness failures.

- Repeat ablation failure, including:
  - More than 1 repeat ablation procedures for AF/AT/ AFL of unknown origin[+] during the 3-Month Blanking Period (Day 0-90 post index procedure).
  - Any repeat ablation procedure for AF/AT/ AFL of unknown origin during the evaluation period.

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- AAD failure:
    - Taking a new AAD (Class I & III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) or taking a previously failed Class I/III AAD at a greater than the highest ineffective historical dose for AF/AFL/AT beyond the 3-month follow-up visit window (i.e., at any time from day 105-365 post index procedure).
- Continuous AF/AT/AFL of unknown origin[+] on a standard 12-lead ECG during the effectiveness evaluation period.
- Any DC cardioversion procedure during the evaluation period for documented atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) recurrences ascertained through protocol specified arrhythmia monitoring methods (12 lead ECG, TTM and Holter).

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead ECG and entrainment maneuvers in an EP study.

9.2.3 Secondary Endpoints

The following hypothesis-driven secondary endpoints will also be evaluated.

9.2.3.1 Secondary Effectiveness endpoints:

- QOL Improvement:
    - Atrial Fibrillation Effect on Quality-of-Life Questionnaire (AFEQT): defined as improvement in total score at 12M post procedure compared to baseline score.

9.2.4 Additional Endpoints:

9.2.4.1 Safety Endpoints

- Incidence of Unanticipated Adverse Device Effects (UADEs)

- Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation
- Incidence of bleeding complication (ISTH definitions): a) major bleeding, b) clinically relevant non-major bleeding and c) minor bleeding.

Refer to Section 14.2.2 for the definition of Serious Adverse Event. Refer to Appendix III: Study Definitions, for the ISTH bleeding complications definitions.

9.2.4.2 Effectiveness Endpoints

The following additional effectiveness endpoints will be assessed:

- Acute procedural success, defined as the percent of subjects with electrical isolation of all PVs with confirmed entrance block at the end of the procedure.
    - Acute reconnection identified by adenosine/isoproterenol challenge.
    - First pass isolation (achievement of entrance block after first encirclement evaluated prior to the 30-min waiting period and adenosine challenge)
    - Ablation by a non-study catheter for PVI (touch-up) among all clinically relevant targeted PVs and by subject
- Repeat ablation procedures
    - Timing (blanking period or after blanking)
    - % PV reconnection by targeted PV and by subject
    - Arrhythmia treated or non-PV targets
- Freedom from documented (symptomatic and asymptomatic) atrial tachyarrhythmia episodes based on electrocardiographic data (≥30 seconds on ECG or sponsor provided TTM or Holter device) during the effectiveness evaluation period (Day 91-Day 365) with the following criteria also deemed failure:
    - Taking any AAD (Class I or III) for AF beyond the 3-month follow-up visit window (i.e., at any time from day 105-365 post index procedure).
- 12 Month Single Procedure Treatment Success off AAD: The 12-month single procedure success is defined as freedom from documented symptomatic AF/AT/AFL (of unknown origin[+]) episodes based on electrocardiographic data (≥30 seconds on ECG or sponsor provided TTM or Holter device) through the effectiveness evaluation period following a single index ablation procedure with all other failure modes included:
    - Acute procedural failure
    - Non-study catheter failure, including:
        - use of a non-study catheter (NSC) to treat pulmonary vein targets/isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) and left atrial non-PV AF targets during the index procedure.
    - AAD failure: Taking a new AAD (Class I & III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) or taking a previously failed Class I/III AAD, at a greater than the highest ineffective historical dose, for AF/AFL/AT beyond the 3-month follow-up visit window (i.e., at any time from day 105-365 post index procedure).

  - Any DC cardioversion procedure during the evaluation period for documented atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) recurrences ascertained through protocol specified arrhythmia monitoring methods (12-lead ECG, TTM and Holter).

- Clinical Success: defined as freedom from documented symptomatic atrial tachyarrhythmia episodes based on electrocardiographic data (≥30 seconds on ECG or sponsor provided TTM or Holter device) during the effectiveness evaluation period (Day 91-Day 365)
- QOL Improvement: Canadian Cardiovascular Society – Severity of Atrial Fibrillation (CCS-SAF): defined as improvement in scores of Class 0 to Class 4 at 12M post procedure compared to baseline scores of Class 0 to Class 4.
- Reduction in Cardiovascular hospitalization rates: defined as reduction in CV hospitalization 6M prior to enrollment compared to 12M post procedure
- Reduction in DC Cardioversion defined as number of DCCV 6M prior to enrollment compared to 12M post procedure
- AAD Utilization by timing: Defined as proportion of subjects on antiarrhythmic drugs by timing compared to baseline

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead electrocardiogram (ECG) and entrainment maneuvers in an EP study

9.2.5 Procedural Data

- Total procedure time, PVI time, PFA application time, mapping time and PFA application time per lesion
- Total Fluoroscopy Time
- Ablation parameters per application
- Device(s) utilized (per ablation)

9.3 Healthcare Utilization Data

Health care utilization pre-, during and post-hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period will be collected. Because this data does not support the safety and efficacy of the VARIPULSE catheter, it will not be provided to the FDA as part of the IDE reporting.

In addition, the sponsor will also collect data associated with follow up care, including any repeat ablation procedure for treating arrhythmia, any inpatient or outpatient visit (including ER admissions, outpatient visits) to address post-procedural complications, any procedure related condition, or any arrhythmia or cardiovascular related conditions.

9.4 Study Timelines

The duration of the study is expected to last approximately 3 years: 6 months for the pilot phase and 2 years for the pivotal phase. The timeline provided below is preliminary and could be revised based on the actual duration of enrollment.

- Pilot Phase:
  - Enrollment will last for approximately 2 months
- Pivotal Phase:
  - Enrollment will last for approximately 12 months.
  - Follow-up duration will be 12 months.

10. Study Population

Patients scheduled to have a clinically indicated ablation procedure for the management of their drug refractory PAF will be screened for enrollment per the study's inclusion and exclusion criteria.

10.1 Subject Selection

The study consists of a PAF population. Subject selection varies is described below.

10.2 Eligibility Criteria

Inclusion Criteria

Candidates for this study must meet ALL of the following criteria:

1. Symptomatic paroxysmal AF with:
   a. At least two (2) symptomatic AF episodes within last six (6) months from enrollment
   b. At least one (1) AF episode electrocardiographically documented within 12 months prior to enrollment. Electrocardiographic documentation may include, but is not limited to electrocardiogram (ECG); Transtelephonic monitoring (TTM), Holter monitor or telemetry strip, and
   c. A physician's note indicating recurrent self-terminating AF within 7 days.
2. Failed at least one (1) AAD (Class I or Class III) as evidenced by recurrent symptomatic AF, intolerable side effects to the AAD, or contraindication to the AAD
3. Age 18-75 years
4. Willing and capable of providing consent
5. Able and willing to comply with all pre-, post- and follow-up testing and requirements.

Exclusion Criteria

Subjects will be excluded from the study if they meet ANY of the following criteria.

1. Previously diagnosed with persistent AF (> 7 days in duration)
2. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., untreated documented obstructive sleep apnea and acute alcohol toxicity).
3. Previous surgical or catheter ablation for AF
4. Patients known to require ablation outside the PV ostia and outside the CTI region (e.g., atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia and Wolff-Parkinson White)
5. Documented severe dilatation of the LA (LAD >50mm) antero-posterior diameter on imaging within 6 months prior to enrollment.
6. Documented LA thrombus by imaging within 48 hours of the procedure.

7. Documented severely compromised LVEF (LVEF <40%) by imaging within 6 months prior to enrollment
8. Uncontrolled heart failure or New York Heart Association (NYHA) Class III or IV
9. History of blood clotting, bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran),
10. Documented thromboembolic event (including TIA) within the past 12 months
11. Previous PCI/MI within the past 2 months
12. Coronary Artery Bypass Grafting (CABG) surgery within the past 6 months (180 days)
13. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, valve repair or replacement and presence of a prosthetic valve).
14. Unstable angina within 6 months
15. Anticipated cardiac transplantation, cardiac surgery, or other major surgery within the next 12 months.
16. Significant pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms.
17. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study
18. Prior diagnosis of pulmonary vein stenosis
19. Pre-existing hemi diaphragmatic paralysis
20. Acute illness, active systemic infection, or sepsis
21. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation.
22. Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm^2)
23. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the IRE energy field.
24. Presence of a condition that precludes vascular access (such as IVC filter)
25. Current enrollment in an investigational study evaluating another device or drug.
26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child-bearing age and plan on becoming pregnant during the course of the clinical investigation.
27. Life expectancy less than 12 months
28. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions for Use (IFU).

10.3 Subject Enrollment and Retention

Study sites will be selected for participation in the study based on experience with single shot (RF or Cryo) catheter technology, ablation experience, their capacity to screen and enroll a reasonable number of eligible patients, and ability to perform the required procedures, according to this protocol.

Historically, women and minorities have been underrepresented in or excluded from many clinical studies, leading to a lack of information for women and their physicians regarding the risk and benefits

of many medical treatments and diagnostic procedures. It is the Sponsor's intent to apply the principles from FDA's guidance titled Evaluation of Sex-Specific Data in Medical Device Clinical Studies in this clinical trial to ensure adequate representation of women and minorities. The Sponsor will take reasonable steps to ensure adequate representation of women and racial or ethnic minorities in this clinical trial including:

In order to reflect the gender ratio of the intended population, Sponsor plans to enroll approximately 70% males and 30% females in the study. The gender ratio (male: female = 7:3) undergoing ablation procedures in the AF population is estimated based on previous studies. [39]

Sites will be instructed to screen all subjects who may be eligible for participation in the study without regard to sex or race. Statistical analysis of primary safety and effectiveness endpoints will be carried out to evaluate any interaction between treatment and gender. Subjects will be encouraged to remain in the study until they have completed the protocol required follow-up period.

Sponsor will attempt to include a diversified group of research sites engaging a variety of academic and private institutions geographically located throughout the US. To ensure generalizability of results and minimize the influence of any single site, no more than 15% of the total enrollment will be allowed at a single site for both study populations.

10.4 Subject Withdrawal/Early Termination

Subjects may withdraw from the clinical investigation at any time. The decision for the subject to withdraw informed consent must be made independently of influence by the investigator or site personnel. The subject's decision will be documented in the source and eCRF. The investigator may also choose to withdraw a subject from the study if there are safety concerns. If a subject withdraws from the study, the date for withdrawal will be recorded on the appropriate electronic case report form (eCRF).

All data will be collected (as available) until the subject is withdrawn. If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the investigator should follow the subject until the AE/SAE has resolved or is considered stable.

Subjects who have signed the ICF but are found to be ineligible PRIOR to insertion of the study catheter will be recorded as screen failures in the eCRF.

10.5 Subjects Lost to Follow-Up

Subjects should be encouraged to return for protocol required, clinic visits for evaluation during the study follow-up period. If a subject is unable to return for an office or clinic visit or unable to be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter to the subject. If the subject does not respond to the letter within 4 weeks, then the subject will be considered "lost to follow-up" for the study.

10.6 Subject Disposition

- **Enrolled Subjects**: subjects who sign the study ICF.
- **Excluded Subjects**: subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will not be included in the primary endpoint analyses and will only be followed between the time of ICF signature and exclusion from the study for adverse event reporting. Subjects who signed the ICF but are found to be ineligible prior to the procedure will be recorded as screen failures in the eCRFs.
- **Evaluable Subjects**: all enrolled subjects who have the study catheter inserted.
- **Discontinued Subjects**: evaluable subjects who have the study catheter inserted but do not undergo ablation (i.e., no PFA energy is delivered with the study catheter). Discontinued subjects will remain in follow-up for 3 months post catheter insertion. If a SAE is reported for a discontinued subject, the subject will be followed until event resolution (with or without sequelae), stabilization, or until the event is adequately explained.
- **Lost to Follow-up Subjects**: subjects who are evaluable, but contact is lost after most recent follow-up visit (despite 3 documented attempts to contact the subject).
- **Withdrawn / Early Termination Subjects**: subjects who withdraw consent for study participation or are withdrawn/terminated from the study by the investigator prior to completion of all follow-up visits.
- **Completed Subjects**: enrolled subjects who have not been excluded, discontinued, withdrawn, terminated early, or lost-to-follow-up prior to the final study visit and have completed the 12-month follow up visit.

11. Responsibilities

11.1 Investigator Responsibilities

The Principal Investigator is responsible for supervision of all study activities and is ultimately responsible for overall compliance with protocol, GCP, local and regional regulations, and IRB requirements. Many study activities may be formally delegated to support staff, but the Principal Investigator retains responsibility for supervision of all study activities.

Specific responsibilities include:

- Obtaining IRB approval and renewals
- Providing Sponsor with:
  - Written IRB approval letters and IRB approved consent forms,
  - Signed, dated Investigator Agreement,
  - Signed and dated Financial Disclosure form at study outset and any time financial changes occur, for up to one year following completion of the study
  - Curriculum vitae for each Investigator and key research staff member
  - Copy of current medical license for each study investigator, as applicable
- Maintaining an accurate and current Delegation of Authority Log which identifies all individuals authorized to perform work for the study at each site

- Completing appropriate training on the study device and the study protocol prior to enrolling and treating subjects
- Maintaining accurate and current logs for the study as requested by the study team, including but not limited to:
  - Subject screening log
  - Device Accountability log
- Obtaining informed consent (including privacy language) from patients prior to subject participation
- Performing the ablation procedure as described in the protocol
- Complying with the clinical protocol
- Notifying the Sponsor and IRB of adverse events, deaths, device failure/malfunctions and deviations as defined in this protocol and per IRB requirements
- Notifying Sponsor promptly of withdrawal of IRB approval
- Complying with IRB (as applicable) and Sponsor annual report requirements
- Completing eCRFs accurately and as soon as possible after collection of data
- Reviewing and signing designated eCRFs in a timely manner
- Maintaining relevant source documentation and allow Sponsor direct access to perform monitoring and auditing duties
- Immediately notify the Sponsor of any pending Regulatory Authority audits/inspection at the study site and allow access to study records for authorized regulatory entities
- Complete all subject follow-up visits, including efforts to maintain contact with subjects who fail to comply with the follow-up schedule. Before a subject may be classified as 'lost to follow-up', the Investigator or authorized personnel should document 3 attempts to contact the subject.
- Retaining study records as described in Section 20.2. The Sponsor will notify the Investigator when records may be destroyed.
- Preparing a final report and periodic IRB updates as required.

11.2 Sponsor Responsibilities

The Sponsor (Biosense Webster) will be responsible for the following:

- Preparing study documents including but not limited to the protocol, eCRFs and template informed consent
- Completing pre-study site assessments and approvals
- Obtaining approval from FDA and regulatory agencies, as applicable
- Obtain signed study contracts from investigators/hospitals, contract research organizations, or other involved parties.
- Providing protocol and device training to investigators and research personnel, as applicable
- Instructing operators and technicians in the proper use and monitoring of study devices
- Monitoring the study throughout the duration of the investigation
- Securing investigator/site compliance with the protocol and applicable regulations
- Creation and maintenance of eCRF database
- Conducting all communications with regulatory agencies

- Submitting study supplements for regulatory approval (e.g., request for study expansion), as necessary
- Preparing reports summarizing the status of the clinical study no less often than annually, which will be supplied to FDA and to other regulatory agencies, as applicable. Annual reports may also be provided to the Principal Investigator
- Preparing and submitting the final clinical study report to FDA and applicable regulatory agencies
- Having AEs reviewed by the study specific committees and/or study specific reviewers, as required
- Report the results of an evaluation of an unanticipated adverse device effect to FDA within 10 working days after receiving notice of the adverse effect.
- Register the study with ClinicalTrials.com no later than 21 calendar days after enrolling the first subject and submit study results on all pre-specified outcomes, including negative outcomes to ClinicalTrials.gov no later than one year after completion of the primary endpoint (unless an extension has been approved via certification from the Secretary of Health and Human Services). Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early.

11.3 Training

11.3.1 Research Team Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or the Sponsor's representative. In some cases, training may be performed by an existing site staff member who has already been trained by the Sponsor (e.g., assigning a new CRC to the study).

Prior to initiating subject enrollment at a site, appropriate study training will be provided. To ensure uniform data collection and protocol compliance, the Sponsor will present a formal educational session to study site personnel that will include review of the Clinical Study Protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, follow-up schedules, and regulatory requirements. Remote as well as on-site contacts will be used to monitor study performance indicators such as enrollment compliance, data submission rate, data errors, protocol questions, and GCP compliance. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

11.3.2 Investigator Training

Prior to initiating subject enrollment at a site, appropriate study training will be provided. Investigators selected to participate in the study will be experienced in intracardiac mapping and AF ablation with focal ablation catheters. In addition to research team training outlined above, Investigators will undergo didactic and hands-on device (VARIPULSE™ Catheter and TRUPULSE™ Generator) training in accordance with the physician training charter.

12. Study Medications

12.1 Antiarrhythmic Drugs

12.1.1 Definitions

- Antiarrhythmic drugs (AADs)
  The study protocol will classify and analyze the following:
  - Class I drugs (e.g., flecainide, propafenone, disopyramide, etc.)
  - Class III drugs (e.g., amiodarone, dronedarone, dofetilide, etc.)
- Previously Failed AAD
  Any AAD that a subject has ever taken for the treatment of his/her AF, prior to enrollment, is considered a "previously failed AAD" if it meets both of the following conditions:
  - prior to enrollment, the AAD was ineffective in controlling the subject's AF or produced intolerable side effects leading to its discontinuation.
  - the AAD is administered for AF
- Contraindicated AAD
  Any AAD contraindicated in the subject due to known medical conditions. The reason for contraindication MUST be documented for each subject
- New AAD
  ANY AAD that was never taken for the treatment of AF prior to enrollment is considered a "new AAD" if the drug is administered to treat atrial tachyarrhythmia episodes post-enrollment.

Table 12.1.1.1 illustrates the corresponding status of primary effectiveness endpoints based on AAD therapy administered in the blanking and post-blanking periods.

Table 12.1.1.1: AAD Usage and Impact on Primary Effectiveness Classification

	Through Three-Month Follow-Up Visit Window (0-104 days post procedure)	**Post-Three-Month Follow-Up Visit Window (105-365 days post procedure)**
Class I and/or Class III AAD	**Can** be initiated, continued from prior to study enrollment, or increased in dose as long as the AAD is **stopped on or before day 104 post procedure** and subject will not be classified as a primary effectiveness failure**.**	If initiated a new AAD for atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) or taking a previously failed Class I/III AAD at a dose greater than the highest ineffective historical dose for AF/AFL/AT; subject will be classified as a primary effectiveness **failure**. **Can** be initiated, continued from blanking period, or increased in dose if drug is used NOT for the treatment of AF/AT/AFL of unknown origin[+] and subject will not be classified as a primary effectiveness failure. The reasons for use of Class I & III AAD other than AF are ventricular arrythmias.
Class II and/or Class IV AAD	**Can** be initiated, continued from prior to study enrollment, or increased in dose and subject will not be classified as a primary effectiveness failure.	**Can** be initiated, continued from prior to study enrollment, or increased in dose and subject will not be classified as a primary effectiveness failure.

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead electrocardiogram (ECG) and entrainment maneuvers in an EP study

Post procedure use of AADs guidelines:

- If Class I & III AAD is initiated through the 3-month follow-up visit window (i.e., day 0-104 post index procedure) , appropriate reason for continuation of the AAD **MUST** be documented and provided in the EDC.
    - The Class I & III AAD **MUST** be discontinued before Day 104 if the AAD was not prescribed for reason of AF/AFL/AT recurrences.
- Post blanking period: New Class I & III AAD MUST only be initiated or dose of the previously failed Class I & III AAD **MUST** be only increased on or before day 104 post-procedure for documented AF/AFL/AT recurrences.
- **Amiodarone use**: Only maintenance dosage will be considered as the highest ineffective historical dose for amiodarone. Use of amiodarone at a dose greater than the historical highest ineffective maintenance dose through the 3-month follow-up visit window (i.e., day 0-104 post index procedure) will be considered as a primary effectiveness failure.
- Use of a Class I or III AAD that was previously not tolerated or contraindicated after the ablation will be considered a **major eligibility deviation**.

12.2 Study Specific Anticoagulation Requirements

- PRIOR to the procedure
  - Uninterrupted anticoagulation management for at least 3 weeks prior to ablation procedure is mandatory for each study subject.
  - For subjects on warfarin/coumadin therapy, subjects must be maintained on warfarin/coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (To be confirmed weekly for 3 weeks prior to procedure. A reading must be taken within 48 hours prior to procedure). Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the study procedure until the INR is ≥ 2 for at least 3 weeks prior to treatment (the subject will need to be reconsented if treatment is scheduled for >90 days after original consent date). The results must be available prior to start of procedure.
  - Anticoagulation therapy should not be interrupted or stopped prior to the procedure (this means no doses should be missed or omitted) and daily regimen should be continued.

NOTE: If a subject is receiving warfarin/coumadin therapy and the anticoagulation therapy is changed to heparin or an equivalent agent, this will be considered continuous anticoagulation therapy and the subject may proceed with the study procedure.

- DURING the procedure – provided in the Study Ablation Procedure section below
- FOLLOWING the procedure
  - Anticoagulation therapy is **REQUIRED** for at least 2 months following ablation.
  - Decisions regarding continuation of systemic anticoagulation beyond 2 months post ablation should be based on the subject's stroke risk profile.
  - Systemic anticoagulation will be continued beyond two months post-procedure in subjects with a CHA2DS2-VASc score of ≥ 2 (unless deemed contraindicated based on clinical considerations).

13. Study Procedures and Evaluations

13.1 Screening and Informed Consent

13.1.1 Patient Screening

All patients considered for PFA ablation procedure for drug refractory recurrent symptomatic PAF should be evaluated by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria.

Subjects are enrolled upon signing the informed consent form. No subject may undergo any protocol required tests or examinations falling outside the standard of care without first signing the Informed Consent form for this clinical investigation.

13.1.2 Informed Consent

The Patient ICFs used must have approval from the Sponsor and the study site's IRB prior to patient enrollment in the stud. An approved Patient ICF may be translated as appropriate. A copy of the blank

approved Patient ICF must be maintained by each investigator in the designated study administrative file.

Signing of an approved Informed Consent form (ICF) or Patient Information/Informed Consent form (PI/ICF) by the study candidate documents the patient's acceptance and enrollment in the study. Prior to signing, the investigator or authorized member of the research team should discuss the background, potential risks and benefits, and expectations of the study with the candidate. The candidate should have any questions answered to his or her satisfaction and should have access to an investigator for technical or medical questions as requested. Sufficient time must be given for this process. The subject or legal representative must sign the consent form prior to conducting any study-specific exams or tests that fall outside of the standard of care. The consent form used must have prior approval from a duly-constituted Institutional Review Board. Failure to obtain informed consent renders the subject ineligible for participation in the study.

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and as required per local regulations. Subject confidentiality will be maintained throughout the clinical trial in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the trial may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

13.2 Pre-Procedure/Baseline Assessments, Evaluations and Procedures

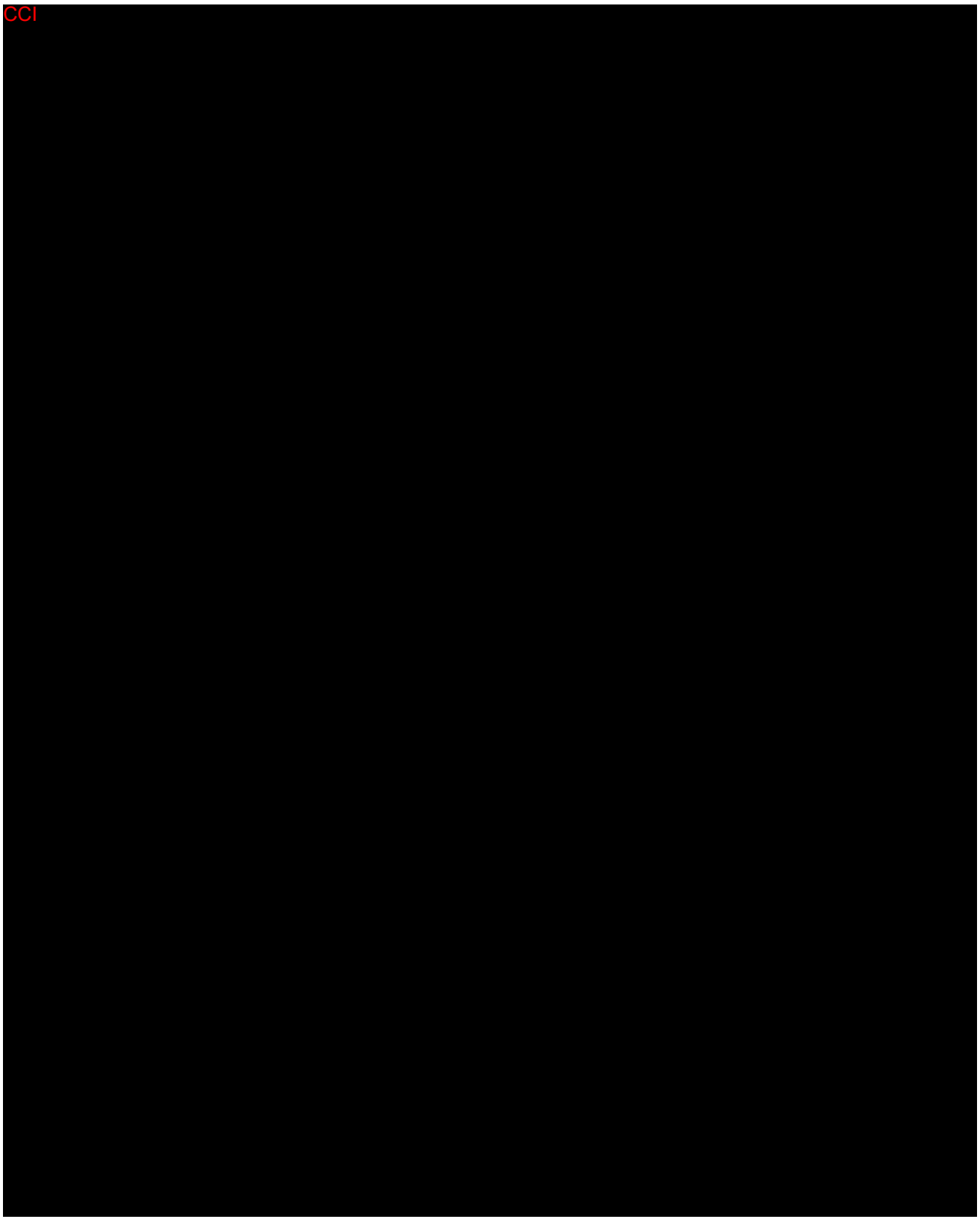
Pre-procedure assessments must be performed within 90 days prior to the index AF ablation procedure unless otherwise noted. The ablation procedure must be performed within 90 days of signing informed consent by the subject. If the ablation procedure is delayed for some reason, the subject must be re-consented.

Assessments with a shorter window prior to the AF ablation procedure are noted below.

- **Demographics** (age, gender, etc.)
- **Medical History**: including but not limited to arrhythmia, heart disease, thromboembolic events, lung/respiratory problems.
- **AF History** (first evidence of AF, number of episodes, symptoms, etc.).
- **NYHA Functional Class Scale** (for subjects with congestive heart failure).
- **CHA2DS2 VASc and $CHADS_2$ Score**: Will be used to assess the risk of stroke
- **Medication History**: Medication history (cardiac medication, AAD medication, anticoagulation regimen and any other clinically significant medication history) shall be gathered by interview or from medical records
- **Anticoagulation Therapy**: Uninterrupted anticoagulation management for at least 3 weeks prior to ablation procedure is mandatory for each study subject. For subjects on warfarin/coumadin therapy, subjects must be maintained on warfarin/coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (to be confirmed maximum 48 hours pre-procedure). Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the

study procedure until the INR is ≥ 2 for at least 3 weeks prior to treatment (the subject will need to be reconsented if treatment is scheduled for >90 days after original consent date).). The results must be available prior to start of procedure. NOTE: If a subject is receiving warfarin/coumadin therapy and the anticoagulation therapy is changed to heparin or an equivalent agent due to documented elevated INR, this will be considered continuous anticoagulation therapy and the subject may proceed with the study procedure even if the INR falls below 2 while the subject is still receiving alternate therapy.

- **Physical Exam** including standardized neurological examination: Exam should be performed by a physician or equivalent (NP or PA) prior to the ablation procedure. The following items will be evaluated as part of the standardized neurological examination: mental status (e.g. orientation, attention, vision, hearing, speech, level of consciousness), cranial nerve testing, assessment of gait and coordination, ability to move all extremities, and evaluation of sensory and motor strength of all 4 extremities.
- **Vital Signs**: height, weight, pulse rate, body temperature, blood pressure
- **Electrocardiogram**: Data from 12-lead ECG recordings will be collected, if available.
- **Imaging to determine LA size and LVEF:** Imaging is required to determine the atrial size prior to the AF procedure. A **Transthoracic Echocardiogram (TTE)** is allowable imaging modality to determine LA size and LVEF. If the subject has undergone an imaging procedure (CT, MRI or ICE or TEE) within the last 6-months where the atrial size (parasternal long axis view) and LVEF were assessed and documented, the pre-procedure imaging assessment is not required.
- **Imaging for detection of LA thrombus** (performed within 48 hours of the study procedure) or day of ablation procedure). The following are allowable imaging modalities:
  - TEE
  - CT/MRI
  - Intracardiac Echocardiography (ICE)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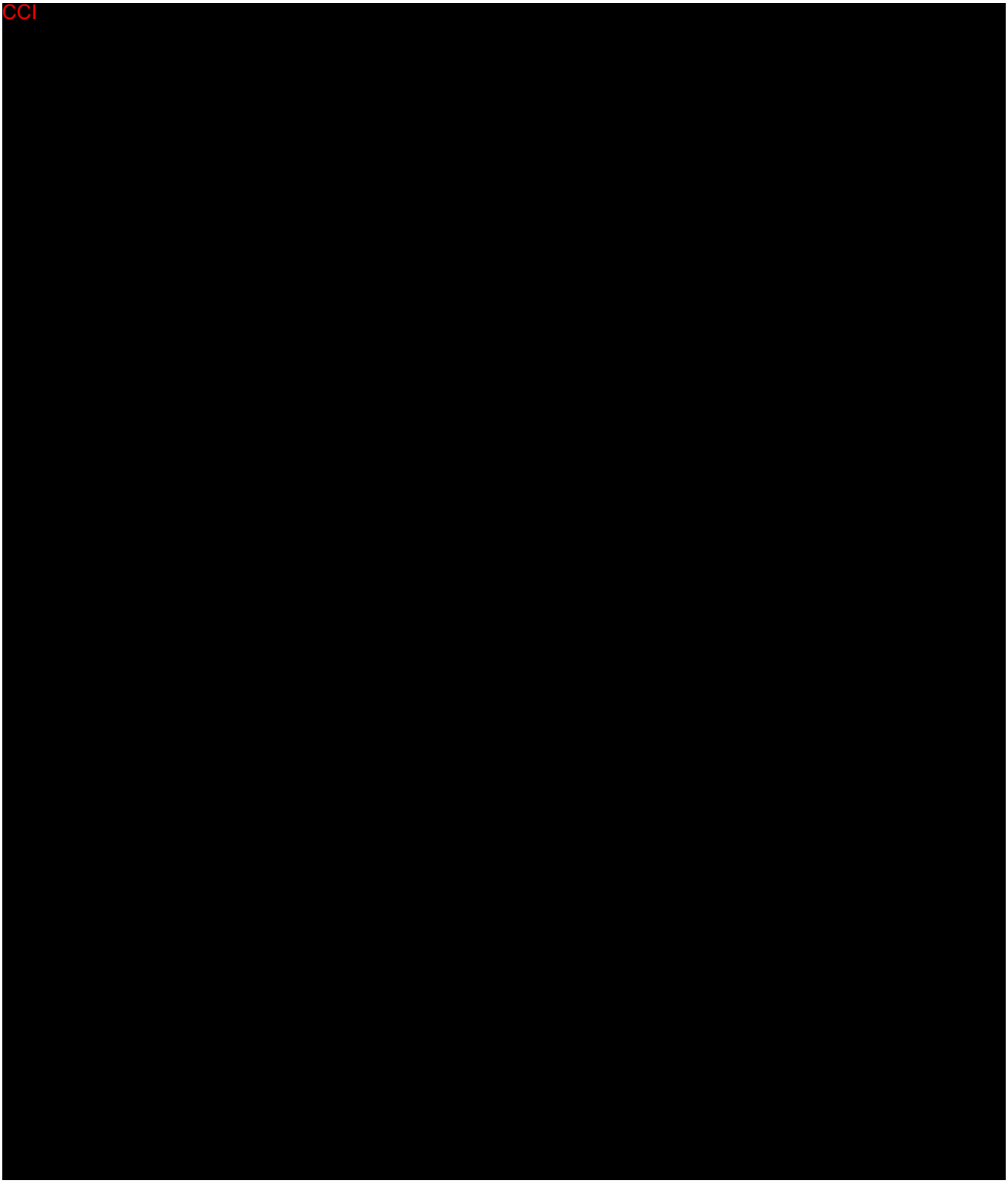
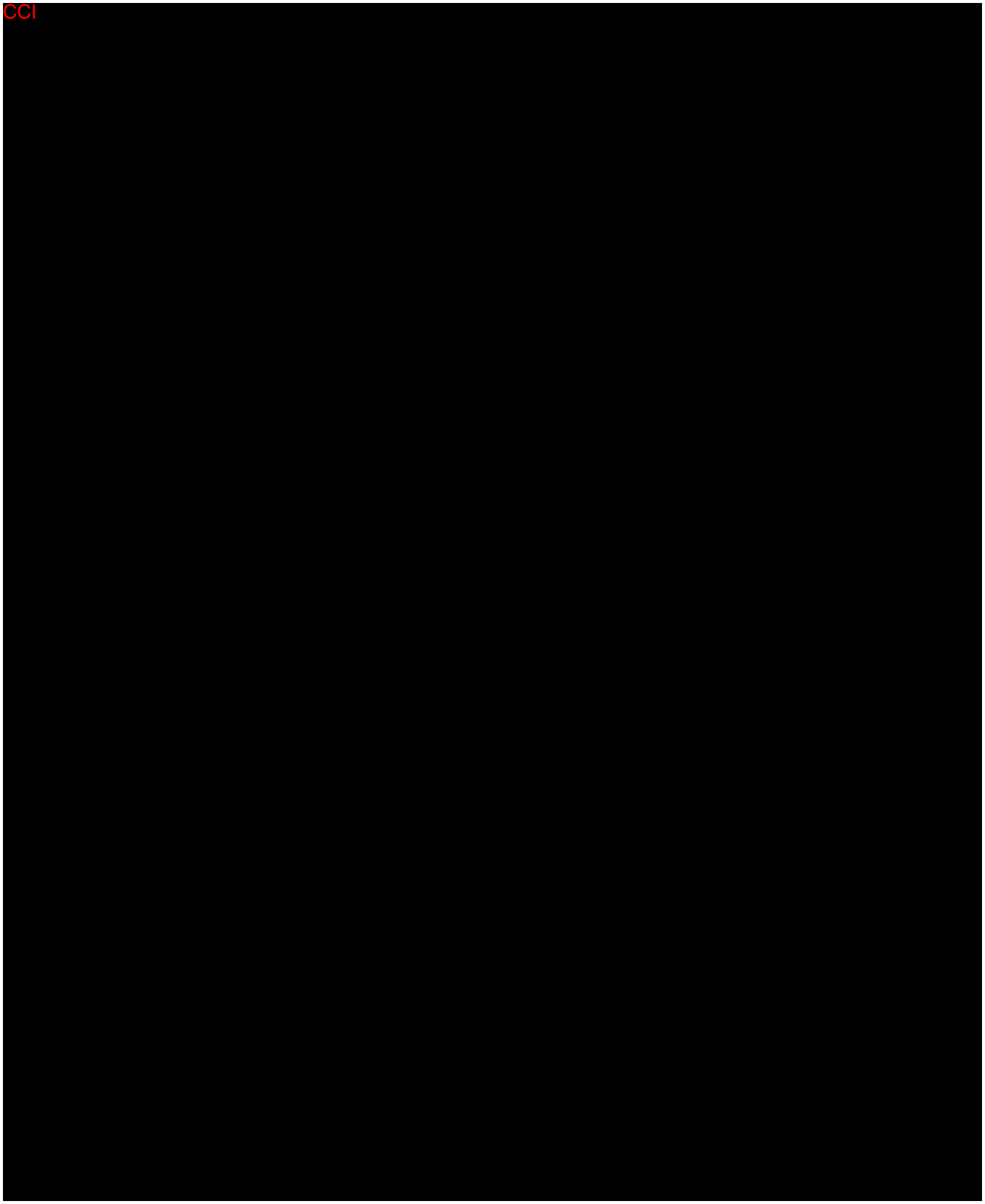



CCl

- Number of PFA applications
- Ablation locations/targets
- Energy delivered
- PFA application time
- Ablation settings
- Procedure time (from first femoral puncture to last catheter out)
- Mapping time (start mapping - end mapping)
- Total fluoroscopy time
- Device deficiency information (if applicable)

Additional data collection for the Pilot Phase only:

- Heparin usage and dosage
- Post procedure, high resolution photographs of all VARIPULSE™ catheters used during a procedure (with scale)
- Catheter dwell time

In addition to the data collected on the CRFs, a back-up of the CARTO™3 file and generator data identified with the subject's study number will be made for each case and are required to be sent to the sponsor as part of the data collection.

13.4 Repeat Procedures

Repeat procedures may be performed at the discretion of the investigator. Repeat procedures for AF/AFL of unknown origin[+]/AT recurrences during the blanking period (0-90 days) MUST be performed using the study catheter for ablating PV reconnections. More than 1 repeat procedure for AF/AFL of unknown origin[+]/AT during the blanking period is considered a failure mode for primary effectiveness. Procedures for CTI dependent flutter in the follow up period are not considered repeat procedures per protocol. Repeat procedures for AF/AFL of unknown origin[+]/AT recurrences during the evaluation period (91-365 days) may be managed per investigator discretion using an approved ablation catheter. The follow-up schedule will remain based on the initial ablation procedure.

For the repeat procedures for AF/AFL of unknown origin[+]/AT recurrences, investigators must collect and provide information on location of reconnections of PVs and in case of atrial flutter recurrence, confirm if CTI dependent flutter or AFL of unknown origin.

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead ECG and entrainment maneuvers in an EP study.

13.5 Post Procedure Follow-Up Assessments

The subjects will be required to complete follow up visits through 12 months (365 days) post initial ablation procedure. Follow-up schedules will be based on a 30-day month.

Follow-up visits should be scheduled according to the following timeframes: 7 day +3 days (7D, day 7-10), 1 month ±7 days (1M, day 23-37), 3 month -14 days (3M, day 76-104), 6 months ±30 days (6M, day 150-210), and 12 month ±30 days (12M, day 335-395). Follow-up visit schedule will not reset if subject undergoes a repeat AF ablation procedure.

The following should be performed prior to hospital discharge:

- Physical exam including standardized neurological examination: Exam should be performed by a physician or equivalent (NP or PA). The following items will be evaluated as part of the standardized neurological examination: mental status (e.g. orientation, attention, vision, hearing, speech, level of consciousness), cranial nerve testing, assessment of gait and coordination, ability to move all extremities, and evaluation of sensory and motor strength of all 4 extremities.
- MUST be performed pre-discharge.
    - If physical exam demonstrates new abnormal neurological findings as compared to the one performed at baseline, a formal neurological consult and examination with appropriate imaging (i.e., DW-MRI) needs to be done to confirm or rule out any suspected diagnosis of stroke.
    - Diagnosis of stroke/CVA must be confirmed by at least one of the following:
        - Neurology or neurosurgical specialist
        - Neuroimaging procedure (MR or CT scan or cerebral angiography)
        - Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)
        - Stroke: (diagnosis as above, preferably with positive neuroimaging study)
            - Minor—Modified Rankin score <2 at 30 and 90 days
            - Major—Modified Rankin score ≥2 at 30 and 90 days
            - MRS assessments should be made by certified individuals
- AFL/AT/AF recurrence
- Electrocardiogram (12-Lead ECG)
- Transthoracic Echocardiogram (TTE), for evaluation pericardium for possible pericardial effusion and/or pericarditis. In the event significant pericardial effusion is identified, subjects should be followed until the condition resolves.
- Cardiac-related concomitant medications (such as AADs, anticoagulation regimen, etc.) All cardiac-related medications prescribed since the ablation procedure till the end of follow-up will be recorded, including the type and name of the medication, associated indications, starting and ending dates of the prescriptions, etc.
- Documentation of Adverse events (if any).

Data collected at the 7 day, 1M, 3M, 6M, and 12M follow-up, and at any unscheduled visits:

- Physical Exam including standardized neurological examination: Exam should be performed by a physician or equivalent (NP or PA). The following items will be evaluated as part of the standardized neurological examination: mental status (e.g. orientation, attention, vision, hearing, speech, level of consciousness), cranial nerve testing, assessment of gait and

coordination, ability to move all extremities, and evaluation of sensory and motor strength of all 4 extremities.. Exam should be performed at all clinical visits.

- Quality of Life questionnaire: AFEQT™ CCS-SAF are to be collected at the 3M, 6M, and 12M visits.
- Electrocardiogram (12-Lead ECG). Data from 12-lead ECG recordings will be collected at the 3M, 6M and 12M follow-up visits. ECG data will be collected at unscheduled visits if completed as standard of care.
- Transtelephonic Monitoring (TTM): TTMs will be provided to each subject no later than at the 1M visit. Subjects will be asked to transmit any symptom-triggered episode that occurs from the time they receive the TTM device through the 12M follow-up visit. Refer to Schedule of Treatments and Evaluations for required transmission schedule. Transmissions should be recorded for a minimum of 60 seconds. A core lab will be used to evaluate and assess the TTM tracings.
- 24 Hour Holter: Holter monitor will be used at the 6M and 12M follow-up visits to monitor the subjects' heart rhythm for 24 hours continuously. A core lab will be utilized to evaluate and assess the 24-hour Holter recordings.
- Cardiac Multi Slice CT/MRA Image: Any subjects who have symptoms suggestive of PV stenosis should undergo CT/MRA imaging.
- Adverse Events: AEs must be collected from the time the subject signs the informed consent onwards.
- AFL/AT/AF recurrence
    - For subjects with AFL recurrence identified through TTM and/or Holter monitoring, a 12 Lead ECG MUST be collected.

- Medication: Changes to any cardiac related medications (cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.) shall be collected
- Repeat Ablation: Any ablation procedure performed after the index procedure will be recorded at 3M, 6M, and 12M follow-up as well as at any unscheduled visits.
- Data for hospitalizations, ER visits and outpatient visits, if any
    - At each follow-up visit, data to be collected may include, but is not limited to:, repeat ablation procedure and/or procedures resulting from the ablation procedure, outpatient visits, and ER visits.
- Subject Completion/ discontinuation form (12-Month).

13.6 Standard Tests and Procedures

The required schedule for subject treatments and evaluations is summarized in Table 13.6.1.

Table 13.6.1: Schedule of Treatments and Evaluations

	Pre-Procedure	Ablation/ Discharge		Phone/ Virtual	Follow-Up Visits				
	Screening / Baseline	Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	1	2	3	4	5	6	7	8	90
Informed consent[1]	X								
Inc & Excl Criteria	X								
Demographics	X								
Vital Signs	X								
Physical Exam including standardized neurological exam	X		X		X	X	X	X	X
Med History[2]	X			X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Hospitalization/ CV history	X								
AF History	X								
ECG	X[3]		X			X	X	X	X[3]
Adverse Events[4,5]	X	X	X	X	X	X	X	X	X
CHA_2DS_2-VASc and $CHADS_2$ Score	X								
NYHA Scale	X								
QOL Assessment[6]	X					X	X	X	
Pregnancy Test[7]	X								
LA size and LVEF imaging	X[8]								
LA Thrombus Imaging		X[9]							
Ablation Assessments		X							
Device Deficiency		X							
TTE		X[10]							
Concomitant Medications[11]	X	X	X	X	X	X	X	X	X
Repeat Ablation					X	X	X	X	X
AF/AT/AFL recurrence			X	X	X	X	X	X	X
TTM [12]					(X)	X	X	X	
24 Hr Holter							X	X	
Completion/ discontinuation form[13]		X	X	X	X	X	X	X	

[1] Initial ablation procedure should be done within 90 days of consent.
[2] Collected to confirm no changes in medical history since last visit
[3] Data from 12-lead ECG recordings will be collected, if available.
[4] AEs collected once consent has been signed. Collected to confirm no changes in health status since last visit. Refer to Table 14.2.1.1 for any additional non-SOC diagnostics required to confirm PAEs.
[5] If AE results in hospitalization, data should be collected.
[6] Quality of life tools (AFEQT and CCS-SAF).
[7] Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.
[8] Imaging should be done within 6 months prior to enrollment.
[9] Subjects must undergo imaging for the presence of LA thrombus within 48 hours of the ablation procedure.
[10] All subjects will undergo TTE prior to discharge to evaluate pericardial effusion
[11] Concomitant medications: only cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.).
[12] Collected weekly starting from 1-month visit through end of month 5 post procedure, (required during the evaluation period, day 91 post procedure) and then required monthly from month 6 post procedure through the end of the evaluation period and during all symptomatic cardiac episodes from the time they receive the TTM device.12-month visit, last completed visit or last data collection
[13] 12-month visit/last completed visit or last data collection

13.7 Unscheduled Visits

If a subject returns for a potential study-related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in Table 13.6.1, the visit will be considered “unscheduled” (UNS). An Investigator may request an unscheduled visit in the presence of a new or worsening cardiovascular condition or neurological deficit. If the unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule is based on the index ablation procedure. For all unscheduled visits, an unscheduled visit eCRF must be completed and the subject must also return for their next scheduled study visit.

13.8 Heart Rhythm Monitoring

ECG, TTM and Holter Monitors will be used to monitor the subjects’ heart rhythm post-treatment.

TTMs:

TTMs will be provided to each subject no later than at the 1-month follow-up visit for scheduled transmissions of heart rhythm status. Subjects will be instructed to transmit following a detailed schedule beginning from their 1-month follow-up visit and during any emergent symptomatic cardiac episodes.

The TTM transmission schedule:

- Subjects will complete a test transmission upon receipt of the TTM device to demonstrate a working understanding of the device.
- Transmissions should be performed once every week starting when the subject receives their TTM (no later than at the 1-month follow-up visit) through the end of month 5 post-procedure (Weekly transmissions are required starting from the evaluation period, 91 days post-procedure through the end of month 5 post-procedure.
- Starting from month 6 post-procedure, subjects MUST record and transmit once every month until the end of the evaluation period, 365 days post-procedure.
- TTM transmission period:
    - Weekly transmissions: 7-day period
    - Monthly transmissions: 30-day period starting after the last weekly TTM window at the end of month 5 post-procedure
- In addition, all emergent symptomatic cardiac episodes from the time the TTM device is dispensed should be recorded and, promptly, transmitted.

Holter Monitors:

Subjects will be provided with a Holter monitor and instructions for the 24-hour recording, no later than at the 6-month follow-up visit. 24-hour recordings will be obtained at the 6-month and 12-month time periods.

13.9 Core Laboratory

A core laboratory will be used to review the TTMs and Holter Monitors for the objective evaluation of recurrence of atrial tachyarrhythmias. Evaluations will be reviewed by a physician. AF/AFL/AT episodes will be evaluated per the definition included in this protocol.

14. Assessment of Safety

14.1 Adverse Event Recording

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) occurring during a clinical study, whether or not related to the study device or ablation procedure.

The following clinical events will not be considered an adverse event for this clinical study:

- Any medical condition that is present at the time of screening. Such conditions should be added to the medical history if not previously reported. However, if the study subject's condition deteriorates at any time during the study, it should be recorded as an AE.

The following clinical events will not be considered an adverse event for this clinical study but will be captured in the database separately:

- Recurrence of pre-existing AF/AT/AFL of unknown origin[+]
- AF/AFL of unknown origin[+]/AT recurrence requiring direct current cardioversion during the blanking period or pharmacological cardioversion (and accompanying hospitalization) at any

time throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE. For subjects with AFL recurrence identified through TTM and/or Holter monitoring, a 12 Lead ECG MUST be collected.

- Re-ablation for AF or pre-existing AFL of unknown origin[+]/AT (including accompanying hospitalization) itself is not an AE, however any complication associated with the repeat ablation procedures is considered an AE and shall be reported within the applicable timelines.

Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., "How has your health been since last visit?"). Anytime during the study, the subject may volunteer information that resembles an AE.

The investigator is responsible for ensuring that all reportable AEs observed by the investigator/study staff or reported by the subject that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the AEs, Unanticipated Serious Adverse Device Effects and Device Deficiencies sections of this protocol and whenever the physician becomes aware of an event. Investigators will determine, at each encounter, whether any adverse events (AE) have occurred, and judge their seriousness and relationship to the study device and procedure. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

All adverse events meeting the above definitions, regardless of classification, seriousness, intensity, outcome, or causality, must be recorded in the electronic CRF(s) in a timely manner throughout the study. Onset date of the event, its treatment, current status (resolved, stabilized, or ongoing), and assessment of its seriousness and relationship to the device should be provided when available. All AEs will be monitored until they are resolved or stabilized (no further changes anticipated).

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead ECG and entrainment maneuvers in an EP study.

14.2 Classification

Any of the following events, and any death or hospitalization while on study, is to be reported to the sponsor immediately. The Sponsor may request additional information after the initial notification.

14.2.1 Primary Adverse Event

A Primary AE is one of the following events occurring within seven (7) days following an AF ablation procedure with the VARIPULSE™ Catheter when used with the TRUPULSE™ Generator per protocol. Table 14.2.1.1 provides the PAEs and their descriptions.

All reported Primary AEs will be monitored until they are adequately resolved or explained.

Table 14.2.1.1: Primary Adverse Events

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Death (device or procedure related)	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Atrio-Esophageal Fistula*	Is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT or MRI scan is the most common method of documentation of an atrio-esophageal fistula.
Cardiac Tamponade,***/Perforation****	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1 cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade should also be classified as "early" or "late" depending on whether it is diagnosed during or following initial discharge from the hospital.
Myocardial Infarction	The presence of any one of the following criteria: • Detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) which persists for more than 1 h • Development of new pathological Q waves on an ECG, and • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Stroke/ Cerebrovascular Accident	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 h; or <24 h, if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)† Confirmation of the diagnosis by at least one of the following: • Neurology or neurosurgical specialist • Neuroimaging procedure (MR or CT scan or cerebral angiography) • Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Stroke: (diagnosis as above, preferably with positive neuroimaging study) • Minor—Modified Rankin score <2 at 30 and 90 days†† • Major—Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography. For the purposes of this study, silent (asymptomatic) cerebral embolism will not be considered a PAE.
Transient Ischemic Attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h. Neuroimaging without tissue injury.
Phrenic Nerve Injury / Diaphragmatic Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when not resolved at the final follow-up.

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Heart Block	Impairment of AV conduction requiring intervention (e.g., temporary or permanent pacemaker) due to iatrogenic cause (e.g., inappropriate RF application, traumatic maneuvering of catheter or other intracardiac devices).
Pulmonary Vein Stenosis+	A reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50-70%, and severe 70% reduction in the diameter of the PV or PV branch. PV stenosis (> 70% PV narrowing) regardless of the presence or absence of symptoms and PV stenosis with ≥ 50% PV narrowing when accompanied with relevant and related symptoms that cannot be explained by other etiologies will be considered a primary adverse event.
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation). Exclusion criteria include: • Pneumonia – infiltrate, fever and leukocytosis • Acute Respiratory Distress Syndrome
Vagal Nerve Injury/ Gastroparesis	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization++++, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.
Pericarditis	Should be considered a major complication following ablation if it results in effusion which leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization++++ by more than 48 h, requires hospitalization++++, or persists for more than 30 days following the ablation procedure.
Major Vascular Access Complication / Bleeding	**Major Bleeding:** A major complication of AF ablation if it requires and/or treated with transfusion or results in a 20% or greater fall in HCT. **Major Vascular Access Complication:** Defined as hematoma, an AV fistula, or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

* Atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure and up to 90 days post-procedure is considered and analyzed as a PAE.

** Cardiac Tamponade/Perforation occurring within 30 days of the AF ablation process will be considered Primary AEs

*** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.
+ Pulmonary Vein Stenosis will be considered as a PAE if it occurs anytime during the 12- month follow up period.
† Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
†† Modified Rankin score assessments should be made by certified individuals.
++++"Hospitalization" means the event necessitated an admission to a health care facility e.g., with at least an overnight stay. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

14.2.2 Serious AEs

A serious adverse event (SAE) is any event that meets one or more of the following criteria:

- Leads to a death
- Leads to a serious deterioration in the health of a subject that:
  - Resulted in a life-threatening illness or injury
  - Resulted in a permanent impairment of a body structure or a body function
  - Required in-patient hospitalization or prolongation of existing hospitalization*
  - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

"Hospitalization" means the event necessitated an admission to a health care facility e.g., with at least an overnight stay. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.
*Planned hospitalization for a condition present prior to the participant's enrollment in the study will **not meet** the definition of an SAE but should nevertheless be included in routine study reporting.

14.2.3 Non-Serious AEs

A non-serious AE is any event that results in minimal transient impairment of a body function or damage to a body structure and does not require any intervention listed under the criteria for "Serious Adverse Event." Non-serious adverse events require routine reporting via EDC.

14.2.4 Anticipated AEs

An anticipated AE is one that has been reported in previous studies of cardiac ablation and can be anticipated in this current study as per the risk analysis. Appendix IV provides a comprehensive list of anticipated AEs. If listed then report event as anticipated.

14.2.5 Unanticipated Serious Adverse Device Effects

A (serious) adverse device effect (SADE) is any (serious) adverse effect on subjects' health, safety, rights, welfare, and life-threatening problems including death, which is caused by, or associated with the study device. Accordingly, relationship to device or study is a crucial assessment by investigators. An

unanticipated adverse device effect (UADE) or unanticipated serious adverse device effect (USADE) is any ADE or SADE that has not been previously identified in nature, severity, or degree of incidence in the study plan or risk analysis report. An investigator shall submit to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation per IRB requirements.

14.3 Clinical Investigation Device Failure/Malfunction/Deficiency

A device has failed if it does not perform according to the instructions for use or fails to meet the expectations of the device and/or investigator (i.e., related to appearance of the device, performance, durability, safety, effectiveness, quality, reliability, labeling, etc.). If a device failure is detected or suspected, it should be documented on the appropriate CRF and the device must be promptly returned according to the Sponsor's instructions. If the device failure is associated with an AE, both the device failure and AE must be reported to the Sponsor immediately upon awareness (refer to Section 14.2).

14.4 Reporting Requirements

All serious AEs, UADE/SADE/USADE, and Study device failure/malfunction/deficiency, whether or not they are related to the device or procedure, must be reported by eCRF to the Sponsor (Biosense Webster Clinical Operations).

The Sponsor is responsible for reviewing AEs (e.g., causality, classification, seriousness) and for ongoing safety evaluations in accordance with the study safety management plan. In case of disagreement between the Sponsor and the principal investigator(s) that remain after query resolution, the Sponsor shall communicate both opinions to the concerned parties.

The Sponsor will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely device-related, probably device-related, or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventive action is required.

Timing for reporting the different types of AEs is described in Table 14.4.1.

Table 14.4.1: Adverse Event Reporting Requirements

Type of Adverse Event	Reporting Requirements
Serious Adverse Events	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
UADE, USADE & SADE	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
Study device deficiency associated with an AE	Report both study device deficiency and AE to Sponsor as soon as possible but no later than 72 hours upon awareness of the event

All other Adverse Events	Routine reporting via eCRF as soon as possible but no later than 2 weeks upon awareness of the event

14.5 Intensity or Severity

Intensity (or severity) of AEs is defined as follows:

Table 14.2.5.1: Intensity or Severity Definitions

Mild	Events that result in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
Moderate	Events that result in moderate transient impairment of a body function or damage to a body structure, or that require intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Events that are life threatening and/or result in permanent impairment of body functions or damage to body structures, or that require significant intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

Intermittent AEs should be classified according to their greatest severity.

14.6 Outcome

AE outcomes are assessed according to the following classifications:

Table 14.6.1: Adverse Event Outcome Classifications

Recovered/ Resolved without Sequelae	Subject fully recovered with no observable residual effects.
Recovering/ Resolving	Subject's condition is improving but residual effects remain.
Recovered/ Resolved with Sequelae	Subject recovered with observable residual effects.
Not recovered/ resolved	AE is ongoing without improvement in overall condition
Fatal	Subject died as a result of the adverse event, whether or not the AE is related to the device or procedure. Note: deaths from any cause occurring on this study are to follow expedited reporting.
Unknown	AE outcome is unknown (e.g., subject lost to follow-up)

14.7 Causality

Causality of AEs is defined as follows:

Table 14.7.1: Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Definitely (Causal Relationship)	The event is associated with the investigational device beyond reasonable doubt
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely
	Not related	Relationship to the investigational device can be excluded
Study Procedure	Definitely (Causal Relationship)	The event is associated with the procedure beyond reasonable doubt.[1]
	Probable	The relationship with the study procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained
	Possible	The relationship with the study procedure is weak but cannot be ruled out completely
	Not related	Relationship to the procedure can be excluded

[1]If event is deemed related to procedure, site should indicate whether related to index or repeat if applicable.

14.8 Documentation

All AEs must be documented on the appropriate eCRF. All AEs must be monitored until they are adequately resolved or stabilized, with follow-up reports submitted to the Sponsor or designee as soon as new information becomes available. For certain events, anonymized documentation, such as a written event narrative detailing the clinical course, copies of correspondence with the local IRB, hospital records, death certificates, and autopsy reports, may be requested by the Sponsor or designee. Follow-up information relative to the subject's subsequent course must be submitted to the sponsor or designee until the event has resolved or, in case of permanent impairment, until the condition stabilizes. If the subject is withdrawn from the study because of the AE, the information must be included on the appropriate eCRFs.

14.9 Safety Oversight

Safety oversight will be conducted as described in the Safety Management Plan. Aggregate safety data will be reviewed regularly throughout the course of the study by the study safety lead or designee to promptly identify new issues or trends which may have an impact on the conduct of the study and/or subject safety.

14.10 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be constituted to monitor subject safety and provide guidance on study adaptation. The DMC charter will document the constitution, roles and responsibilities of the committee. Under the rules of an approved study-specific charter, safety data will also be reviewed by an established DMC which may recommend appropriate action(s) to ensure subject safety.

14.11 Clinical Events Committee

A Clinical Events Committee (CEC) will be implemented to adjudicate the primary safety endpoint events. The CEC will operate as described in the CEC Charter.

15. Deviations from the Clinical Study Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures described in this protocol except in medical emergencies. A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (e.g., missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria). Investigators are not allowed to deviate from the protocol. Protocol deviations will be monitored closely and may require reporting to the IRB and/or regulatory authority per IRB/regulatory authority requirements.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed. Such deviations shall be documented as protocol deviations in the eCRF and reported to the IRB/regulatory authority as required.

In emergencies, prior approval for a protocol deviation will not be required, but the Sponsor clinical operations personnel should be notified as soon as possible. The study monitors shall verify that the conduct of the study is in compliance with the currently approved protocol and applicable regulations and shall identify any issues of non-compliance with regulations or guidelines. Issues of non-compliance include but are not limited to repeated protocol deviations, failure to obtain proper informed consent, non-conformance to IRB requirements, and failure to report any event requiring expedited reporting. IRB must also be notified promptly of significant protocol deviations as they are defined by the IRB.

Non-compliance and issue escalation will be addressed per the study Project Operations Manual, TV-eFRM-02873.

16. Investigational Device Accountability

16.1 Investigational Device Acquisition and Accountability

The study site will receive the necessary amount of study-related materials prior to commencement of study ablation procedure. Study-related devices (investigational and non-investigational) will be shipped to the site after completion of required documentation (essential regulatory documents, Clinical Trial Agreement, IRB approval, regulatory agency approval) and training. Investigational study devices are only to be used for subjects enrolled in this clinical study. Study-related materials may be augmented throughout the study on an as-needed basis.

The Sponsor will label all devices as “Investigational Device” (as applicable for the region) in a prominent location. All system installations will be performed by trained field services personnel according to internal processes.

The Sponsor will keep records of all investigational devices shipped to the site. Investigator site personnel are responsible for ensuring appropriate device logging is completed.

The site Device Accountability Log will include the following information:

- Date of receipt
- Individual acknowledging receipt
- Quantity received
- Packing Slip Verification
- Catalog number for catheters
- Serial/lot numbers
- Expiry Date
- Dates devices were used
- Subject IDs for whom devices were used
- Date of return (as applicable)
- Type of disposal (i.e., return to Sponsor for adverse event, complaint, expired, end of study, etc.).

16.2 Investigational Device Returns

All study devices **(used and unused)** must be returned to the Sponsor. Devices suspected of a deficiency or devices associated with a (device related or possibly related) adverse event, should be returned immediately to the Sponsor and will undergo thorough analysis. All shipping and tracking information should be retained. Returned devices must be decontaminated per hospital policy and labeled with the following information:

- Study name (AdmIRE)
- Subject identification number, or if unused, site number
- Date of use/event or if applicable, specify "unused"
- Return type (device deficiency related, AE related, etc.).

17. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Each site will undergo periodic monitoring of the study, which involves a visit from a trained Sponsor representative. Monitoring visits may include, but will not be limited to, the following:

- Adherence of the protocol
- Verification of accuracy of study logs such as the Delegation of Responsibility, etc.
- Verification that informed consent is obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the Regulatory Binder.
- Source data verification with the eCRFs.
- Identification and action to resolve any issues or problems with the study.

Data are to be submitted as soon as possible after collection via eCRF. Missing or unclear data will be corrected as necessary throughout the trial. The Sponsor may request further documentation such as physician and/or cardiac EP lab procedure notes when complications or malfunctions are observed and reported. Data submitted on eCRFs will be verified against source documents (medical records) utilizing the principles specified in FDA's guidance on risk-based monitoring (Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring) and will be detailed in the **Monitoring Plan**.

Remote data monitoring may be utilized for sites where remote electronic medical record (EMR) access may be granted by the institution to the assigned sponsor study monitor, in alignment with both institution and sponsor mandated processes. Remote monitoring options may also include clinical sites providing de-identified and HIPAA compliant source documents and screen sharing (via Teams, WebEx, etc.) to the monitors.

Monitoring activities will be documented through such means as contact reports and follow-up summaries of status and action items. Further details on clinical monitoring are provided in the study specific monitoring plan.

17.1 Early Termination Monitoring Visit

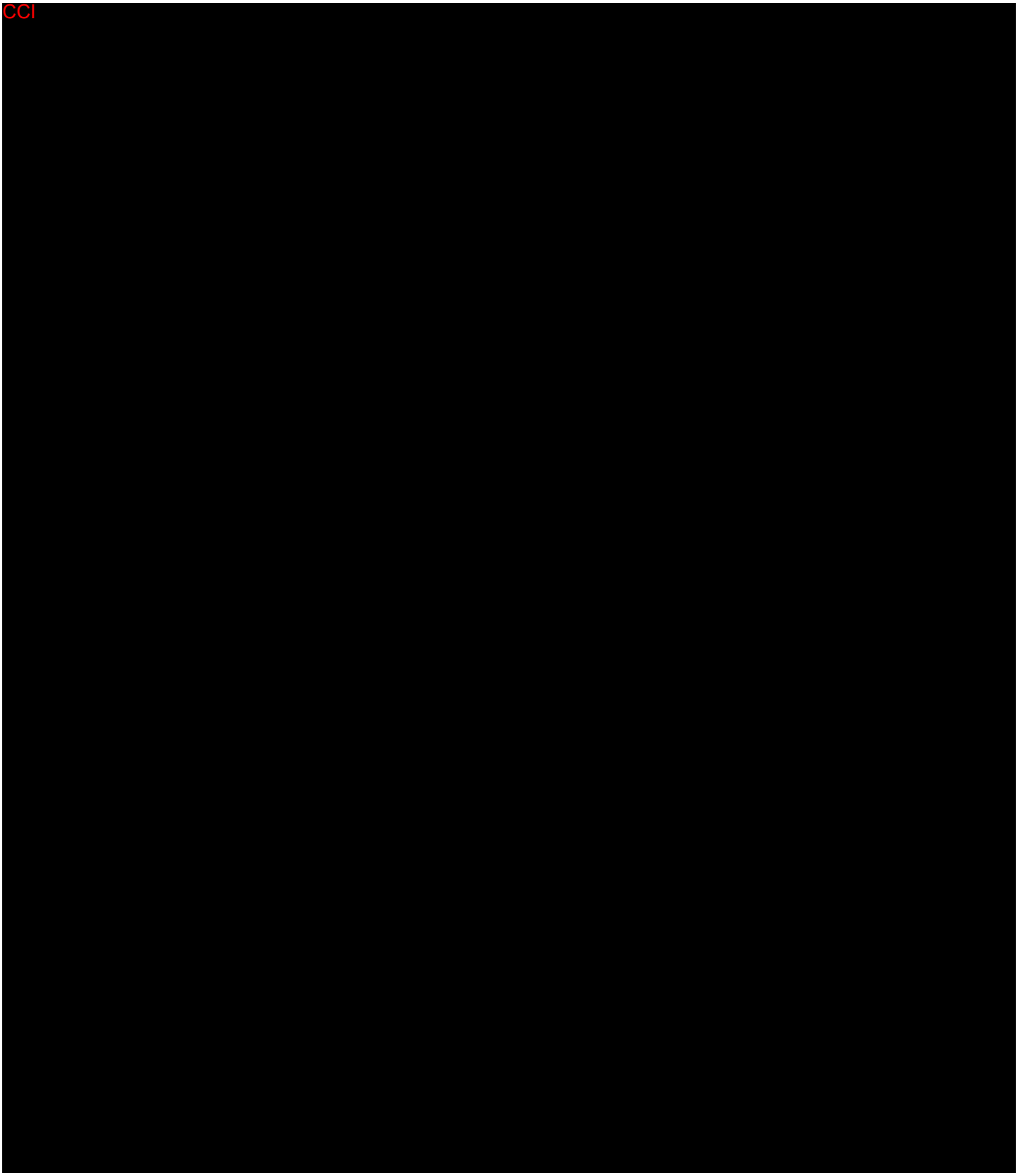
If early termination of the study is required, each site will undergo a monitoring visit as described in the monitoring plan to conclude any outstanding issues, collect all outstanding CRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study. Subjects will be notified of the termination of the study. Any enrolled subjects will continue to be followed per the study protocol requirements until a study closeout plan is implemented that outlines alternative follow-up procedures.

18. Statistical Methodology

The Sponsor will be responsible for the overall analysis of data from this protocol. A separate Statistical Analysis Plan (SAP) will be written and approved prior to database lock. The SAP will describe all planned analyses based on the statistical design of this study and the subsequent data collected. A brief statistical overview of key statistical analyses is provided below.

This clinical investigation is a prospective, multicenter, non-randomized, premarket clinical evaluation of the BWI IRE Ablation System (VARIPULSE™ Catheter and TRUPULSE™ Generator) to demonstrate safety and long-term effectiveness when compared to performance goals.

The trial will enroll 20 subjects in the pilot phase and up to 248 subjects (225 evaluable with 10% attrition but not including roll-ins) will be enrolled in the pivotal main phase. The pilot phase will be used to characterize the safety profile of the BWI IRE Ablation system. The preliminary estimates for safety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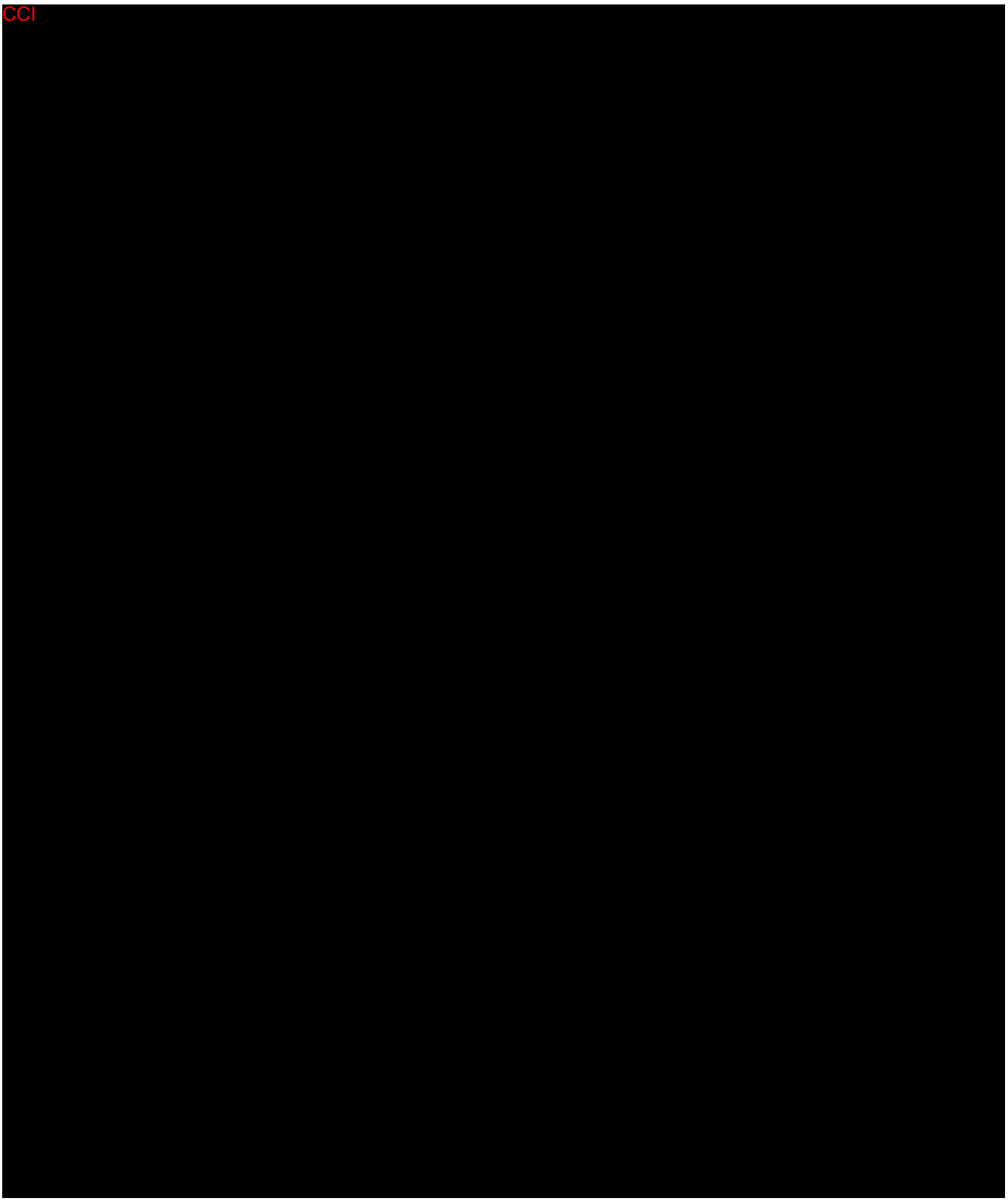
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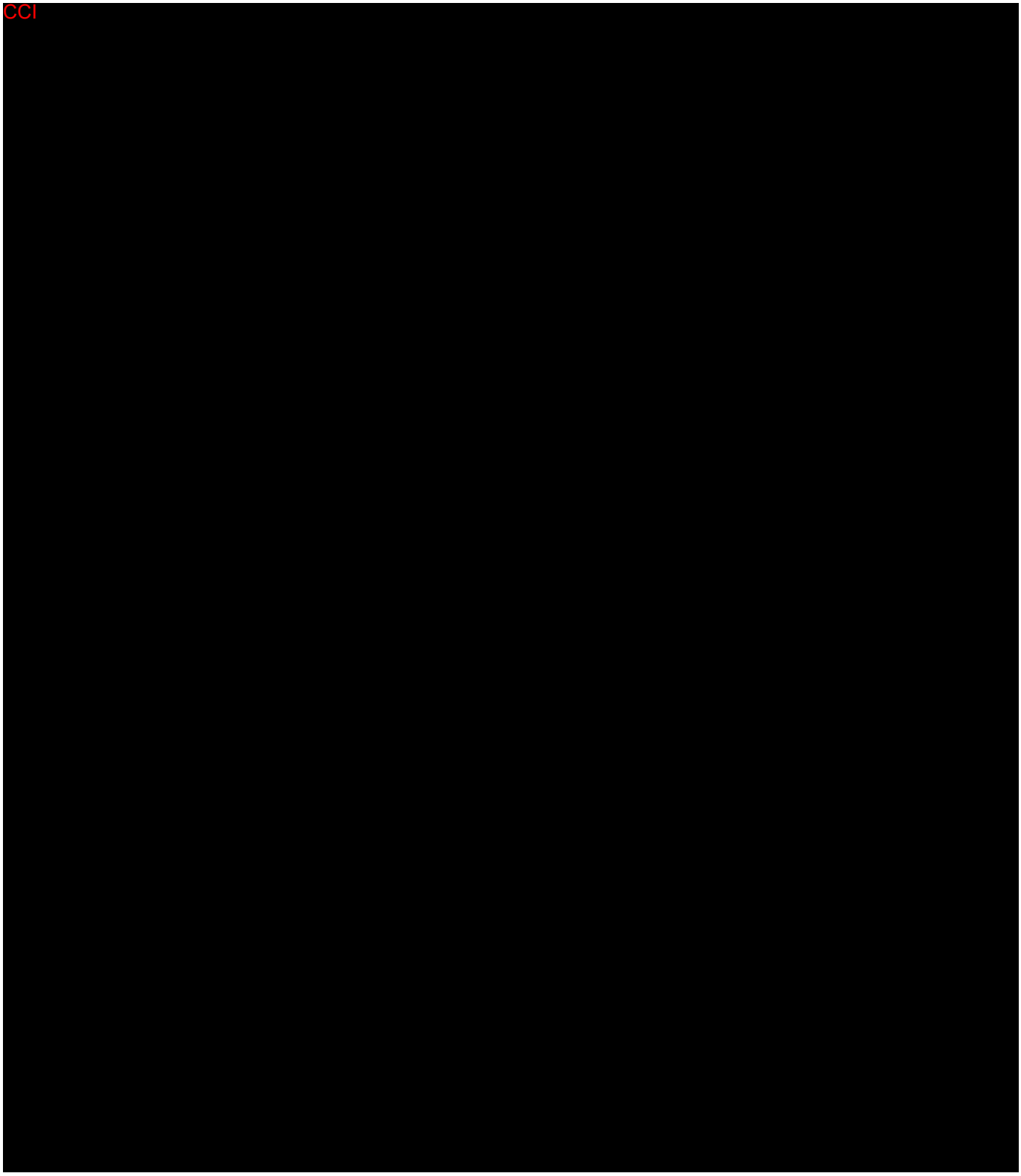
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Study materials including informed consent, survey questionnaires, and any proposed advertising or recruitment materials must be reviewed and approved by an appropriately constituted IRB before enrollment of subjects. The Sponsor and the IRB must approve in writing any changes to the protocol, informed consent documents, and other study documentation referenced above.

Proof of IRB review and approval must be obtained prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local regulations) of the study by their IRB.

19.2 Ethical Standard

As the Sponsor of this study, Biosense Webster has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration and the local government. The Sponsor will also maintain compliance with the International Conference for Harmonization Good Clinical Practice (ICH-GCP), regulations, guidelines, and applicable standards.

19.3 Informed Consent Process and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation.

Discussion of risks and possible benefits of participation will be provided to the subjects as part of the informed consent process. Consent forms will be IRB approved and the subjects will be asked to read and review the document. The investigator, or designee, will explain the research study to the subjects and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. The investigator, or designee, will explain that any new information that develops over the course of the study will be provided to the subject in a timely manner. Information should be given to the subjects in a language and at a level of complexity understandable to the subjects in both oral and written form by the principal investigator or designee. Subjects will have ample opportunity to review the written consent form and to ask questions prior to signing.

Prior to participation in the trial, the ICF should be signed and personally dated by the subject or his/her legal representative. If a witness is used for an illiterate subject, the witness should also sign the consent form, attesting that informed consent was freely given by the subject or his/her legal representative. The subject may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A signed and dated copy of the ICF must be collected from each enrolled subject and kept in the study subject files and medical records. The site should provide each subject with a copy of their fully executed ICF.

Remote- and e-consenting is permissible with prior approval by Sponsor and in compliance with the site's IRB policy,

The Sponsor and the reviewing IRB must approve any modifications to the ICF for this clinical investigation. A copy of the IRB approved ICF must be maintained by each investigator.

Documentation of the consent process for each subject should be maintained in their medical record by each investigator.

Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial.

19.4 Confidentiality

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. Only authorized Sponsor personnel or representatives, or representatives of Regulatory Authorities (RA) acting in their official capacities will have access to these confidential files. No data transmitted to Sponsor for evaluation and reporting will contain identifiable references to individual subjects.

19.5 Subject Confidentiality/Record

All representatives of the Sponsor have undergone training for Privacy regulations and appropriate conduct for their compliance. For the duration of this study, all representatives of the Sponsor will comply with all privacy regulations regarding contact with subjects, their medical record information, copying of information, protection of the subject identities, and other aspects. Authorization for limited

access to Protected Health Information by Sponsor personnel will be obtained as part of subject informed consent.

Site personnel should also be attentive to privacy considerations and should not transmit PHI outside of PI control (e.g., via .pdf scans) without redaction of patient identifiers.

Privacy considerations such as above will also be covered in protocol training for both Sponsor representatives and study site personnel.

20. Data Handling and Record Keeping

20.1 Data Collection and Management Responsibilities

The Sponsor will be responsible for all data management activities. These activities include development of an electronic data collection (EDC) system and utilizing a validated EDC system into which all study data will be entered. The Sponsor will be responsible for reviewing all data to ensure the overall integrity of the database.

20.1.1 Data Collection

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during this clinical investigation. eCRFs have been developed to capture the information outlined in this protocol. Modification to the eCRF will only be made if deemed necessary by the sponsor. Data on these eCRFs will be monitored (source verified) and corrected, if necessary, to match the source documents. Changes made to the data will be tracked in the electronic audit trail. The investigator will be required to sign designated eCRFs as verification that they have been reviewed and the data entered are correct. Data from these eCRFs will be sent to the Sponsor, and/or 3rd party affiliate acting on behalf of the Sponsor and used in the analysis of clinical investigation results.

At the completion of the study ablation procedure, two back-up copies of the CARTO™3 and generator log files will be made. One copy should be kept at the site within the investigator site or subject binders, and one fully anonymized copy will be provided to/collected by the Sponsor.

20.1.2 Source Documentation

Data entered into the eCRFs must be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or office document exists to capture some of the information that may be unique to this study, a worksheet may be developed to record this information. Data collection instruments should clearly identify the individual collecting the data and the date of collection. The instrument of original capture of all study data will serve as the source document for future verification of those data parameters. Privacy regulations will be observed during the use of these source documents during monitoring.

Investigators should maintain information in the subject's medical records, which corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained.

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol selection criteria (if not already present).
- Dated and signed notes from the day of entry into the study including the study Sponsor (Biosense Webster), protocol number, clinical site, subject number assigned and a statement that consent to participate in the study was obtained.
- Dated and signed notes from each study visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).
- Reports on AEs and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, lab results.
- Notes regarding protocol-required medication and prescription medications taken during the study (including start and stop dates).
- Notes on subject's condition upon completion of or withdrawal from the study.

20.1.3 Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are properly recorded on each subject's eCRF and related documents. Completed eCRFs will be reviewed and monitored by the Sponsor personnel, or an appropriately qualified and trained designee, throughout the clinical investigation. To this end, the Investigator and institution must permit inspection of the trial files including original (source) records and subject eCRFs by Sponsor representatives and/or responsible government agencies.

It is recommended that all eCRF data be entered by the designated site personnel as soon as possible. It is the responsibility of the investigator to provide timely completion of eCRFs, including procedural data, for review by the Sponsor. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines noted within this clinical protocol (Section 14.4).

Investigators are required to prepare and submit accurate and timely reports on this study to the Sponsor and governing IRB, if necessary, per Table 20.1.3.1.

Table 20.1.3.1: Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator For	Time of Notification
Subject withdrawal	Sponsor	Should report within 5 working days
Withdrawal of IRB approval	Sponsor	Should report within 5 working days
Final report	Sponsor, IRB	Will prepare a final report for the clinical investigation as required per national regulations.
Informed consent not obtained from subject	Sponsor, IRB	Should report to Sponsor within 5 working days Should report to IRB per local requirements

Upon completion or termination of the Sponsor study, the principal investigator must submit a final written report to the approving Investigational Review Board (as required by the IRB) and provide a copy to the Sponsor. The report should contain the information required by the IRB and be submitted in the time frame required by the IRB.

20.1.4 Data Review

The Sponsor will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments. Missing or unclear data points will be queried as necessary throughout the trial. The Sponsor may request further documentation such as physician and/or cardiac EP lab procedure notes when complications or device deficiencies are observed and reported. The Sponsor will be responsible for auditing the database and confirming the overall integrity of the data.

20.1.5 Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

20.2 Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 2 years or per country specific record retention requirements following notification by the Sponsor that all investigations have been terminated or completed. Records for U.S. sites must be maintained in accordance with 21 CFR 812.140 [d], and for OUS sites, according to local requirements. This documentation must be accessible upon request by the regulatory authorities, the Sponsor, or a designee. The Sponsor must approve archiving, transfer, and destruction of the documentation, in writing, prior to the actual archiving, transfer, and destruction. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing the study documentation.

If the investigator retires, relocates, or withdraws from assuming primary responsibility for keeping the study records, custody transfer per written notice must be submitted to the Sponsor indicating the name and address of the person accepting primary responsibility. The IRB must be notified in writing of the name and address of the new custodian.

Records and reports may be discarded upon notification by the Sponsor to the study site. Site personnel should contact the Sponsor prior to destruction of any study-related records and reports to ensure appropriate record retention.

20.2.1 Records

Records to be maintained by the investigator include:

- Study protocol and all amendments with signature pages
- Signed clinical study agreement and Statement of Investigator
- IRB approval letters, including approved ICF documents
- Evidence of IRB compliance
- Other significant IRB correspondence

- Significant sponsor correspondence relating to the study
- CVs for all investigator(s)
- Financial Disclosure for key study staff
- Records of protocol and supporting training
- Site personnel delegation of authority/responsibility log
- Clinical Monitor/Site Visit sign-in log
- Device accountability log
- Reports (e.g., annual reports, final reports from investigator and Sponsor).

The following records must be maintained for each subject enrolled in the study:

- Signed Patient ICF
- All completed electronic CRFs and supporting source documentation
- Supporting documentation of any AEs and/or death.

The investigator must retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur while the subject is enrolled in the study. The Sponsor reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study.

21. Clinical Compliance and Quality Control

Quality Control (QC) procedures will be implemented beginning with the data entry system, and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. If noncompliance is identified, Sponsor is required by regulation to implement measures to secure compliance.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

22. Study Suspension or Termination

The study may be suspended or terminated early at the discretion of the Sponsor, for reasons such as incidence of unanticipated serious adverse device effects that may pose a risk to other subjects. In any early termination, already enrolled subjects will continue to be followed per the study protocol requirements.

Sponsor may also terminate a site prior to completion if it believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by IRB).

At termination of the investigation, each active site will undergo closeout monitoring to conclude any outstanding issues, resolve all data discrepancies and make sure any outstanding eCRFs are completed, discuss responsibilities with the Principal Investigator, and discuss any other items relevant to the conclusion of the study. The termination process will be documented by a written report.

23. Data and Publication Policies

Publications and/or presentation of clinical investigation results will be coordinated between the Sponsor and the clinical investigation author(s). Authorship will be determined prior to development of any manuscript. All information concerning the study, investigational medical device, Sponsor operations, patent application, 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.

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25. Appendices

25.1 APPENDIX I. List of Acronyms and Abbreviations

AAD	Antiarrhythmic drug	ICF	Informed consent form
ACT	Activated clotting time	IFU	Instructions for use
AE	Adverse event	IRB	Institutional Review Board
AF	Atrial fibrillation	ITT	Intent-to-treat
AFL	Atrial flutter	HIPAA	Health Insurance Portability and Accountability Act
AHA	American Heart Association	LA	Left atrium
ANOVA	Analysis of variance	MI	Myocardial infarction
AT	Atrial tachycardia	MRI	Magnetic resonance imaging
AV	Atrioventricular	MV	Mitral valve
BP	Blood pressure	NSC	Non-study catheter
CCS-SAF	Canadian Cardiovascular Society-Severity of Atrial Fibrillation	PAF	Paroxysmal atrial fibrillation
CEC	Clinical Events Committee	PCI	Percutaneous coronary intervention
CHF	Congestive heart failure	PIU	Patient Interface Unit
CF	Contact force	PP	Per protocol
CFAE	Complex fractionated atrial electrogram	PV	Pulmonary vein
CHADS	Congestive heart failure, High blood pressure, Age 75+, Diabetes, previous Stroke or transient ischemic attack	PVI	Pulmonary vein isolation
CPVI	Complete pulmonary vein isolation	QOL	Quality of life
CRF	Case Report Form	RA	Right atrium
CS	Coronary sinus	RF	Radiofrequency
CT	Computed tomography	SADE	Serious adverse device effect
CTI	Cavotricuspid isthmus	SAE	Serious adverse event
CVA	Cerebrovascular accident	SAP	Statistical analysis plan
DMC	Data Monitoring Committee	SF	Surround Flow
ECAS	European Cardiac Arrhythmia Society	SOC	Standard of care
EPU	External processing unit	SOP	Standard operating procedure
ESC	European Society of Cardiology	SVC	Superior vena cava
FDA	Food Drug Administration	TIA	Transient ischemic attack
GCP	Good Clinical Practice	TEE	Transesophageal echocardiogram
ECG	Electrocardiogram	TTE	Transthoracic echocardiogram
EHRA	European Heart Rhythm Association	TTM	Transtelephonic monitoring
HRS	Heart Rhythm Society	UADE	Unanticipated adverse device effect
ICD	Implantable cardioverter defibrillator	USADE	Unanticipated serious adverse device effect
ICE	Intracardiac echocardiography	VT	Ventricular tachycardia

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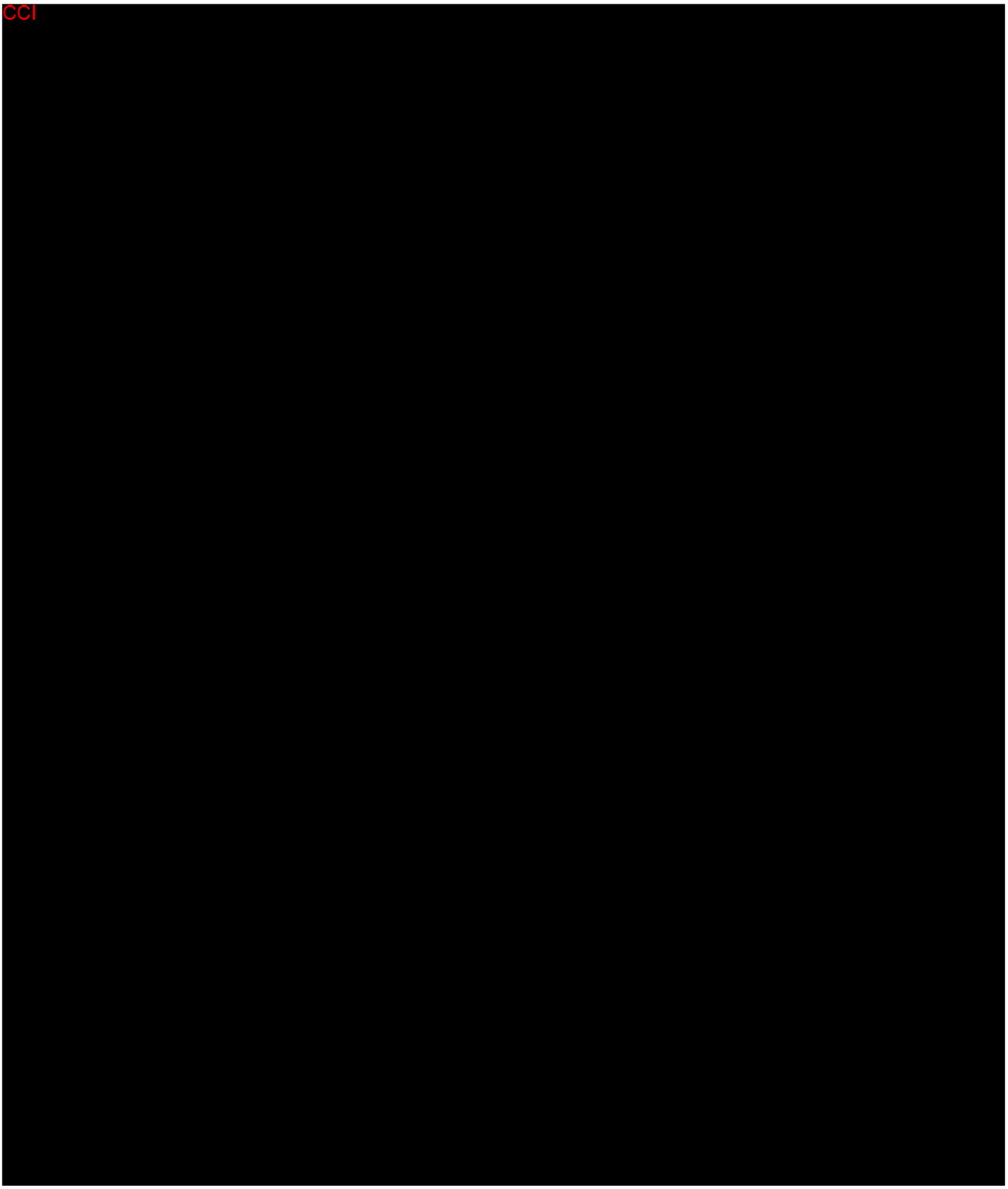

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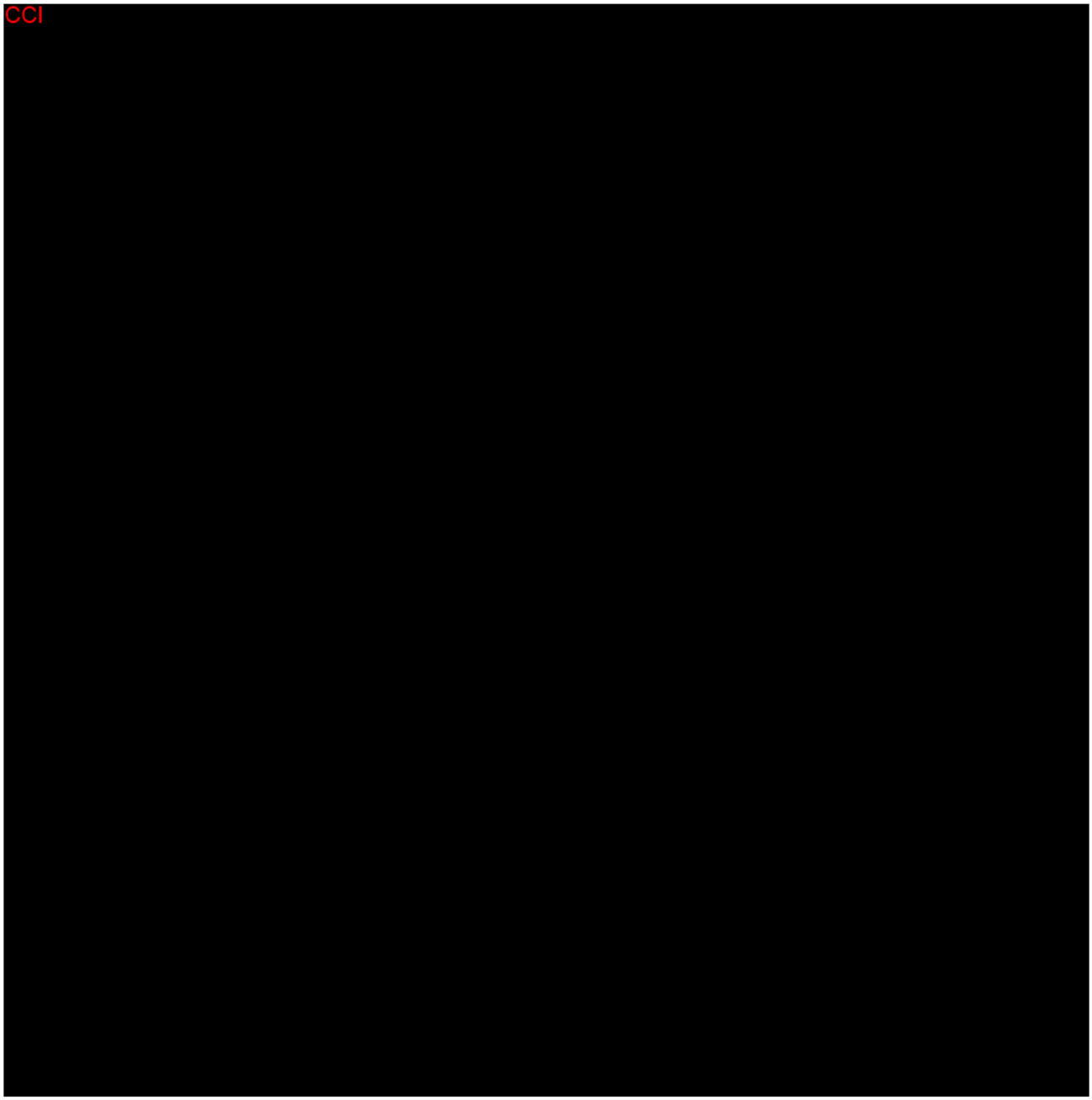

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25.3 APPENDIX III. Study Definitions

Term	Definition
Adverse Event (AE)	Any unfavorable and unintended sign, medical occurrence, disease or injury (including abnormal laboratory findings) in subjects, users or other persons temporally associated with the use of a medicinal product or device whether or not related to the sponsor's product. This definition includes events related to the medical device and/or the comparator, and events related to the procedure in which the device was used.
Adverse Device Effects (ADE's)	Adverse events related to the use of the medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use deployment, implantation, installation, or operation, or any malfunction of the medical device. This definition includes any event resulting from use errors or from intentional misuse of the investigation medical device.
AF/AT/AFL of unknown origin Episode	An episode of AF/AT/AFL of unknown origin[+] ≥ 30 seconds in duration.
AF Episode	An atrial fibrillation episode is defined as AF which is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be documented by ECG monitoring between AF episodes
Anticipated AE	An effect which by its nature, incidence, severity or outcome has been identified as possible complications associated with the medical device and/ or intervention procedure.
Atypical Flutter	Macro-reentrant circuits within the atria where activation rotates around large obstacles that does not meet the criteria for Typical Flutter.

Term	Definition
Bleeding Complications (ISTH definition):	Major (ISTH definition): Fatal bleeding AND/OR symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome AND/OR bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of blood. Clinically relevant nonmajor bleed (ISTH definition): An acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response such that it leads to one of the following: hospital admission for bleeding; physician guided medical or surgical treatment for bleeding; change in antithrombotic therapy (including interruption or discontinuation). Minor bleeding (ISTH definition): All nonmajor bleeds. Minor bleeds are further divided into clinically relevant and not.
Catheter Insertion	Defined as the VARIPULSE™ Catheter breaching the sheath and entering the bloodstream.
Device Deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction (failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol), misuse or use error and inadequate labeling.
Documented AF/AT/AFL of unknown origin episode	An AF/AT/AFL of unknown origin+ episode documented by an electrocardiographic monitoring tool. This may include ILR, ECG, TTM, Holter monitor, or telemetry strip. Reporting of a symptomatic episode by a patient or in a referral letter is not considered a documented AF episode.
Minor Pericarditis	Pericarditis will be considered 'minor if is treated using only analgesics and does not extend hospitalization by more than 48 hours.
Paroxysmal AF	Paroxysmal AF is defined as recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤ 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.

Term	Definition
Permanent AF	Not appropriate in the context of patients undergoing catheter ablation of AF; refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation.
Persistent AF (PsAF)	Persistent AF is defined as continuous AF that is sustained beyond 7 days and less than 1 year.
Serious adverse event (SAE)	1. Any adverse event that: • Led to a death • Led to a serious deterioration in health that either: o Resulted in a life-threatening illness or injury, or o Resulted in a permanent impairment of a body structure or a body function, or o Required in-patient hospitalization or prolongation of existing hospitalization, or o Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death or a congenital abnormality or birth defect 2. Any Device Deficiency that could have led to an SAE A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.
Serious Adverse Device Effects (SADEs)	Adverse device effects that have resulted in any of the consequences characteristic of a serious adverse event.
Symptomatic AF/AT/AFL of unknown origin[+] Episode	Symptom(s) which is/are exhibited by the subject which made them seek medical attention and are concurrent with a documented episode of AF/AT/AFL by either ECG, TTM, Holter monitor, or telemetry recording. Symptoms may include but are not limited to: palpitations, irregular pulse (e.g., rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.

Term	Definition
Typical Flutter	Atrial flutter is caused by a reentrant rhythm in either the right or left atrium. Typically initiated by a premature electrical impulse arising in the atria, atrial flutter is propagated due to differences in refractory periods of atrial tissue. This creates electrical activity that moves in a localized self-perpetuating loop. For each cycle around the loop, there results an electric impulse that propagates through the atria.
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 SADE: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report
Ventricular Tachycardia (VT)	Ventricular tachycardia: a tachycardia (rate $\geq$ 100/min) with three or more consecutive beats that originates from the ventricles independent of atrial or AV nodal conduction. Continuous VT for $\geq$ 30 s or that requires an intervention for termination (such as cardioversion).

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead ECG and entrainment maneuvers in an EP study.

APPENDIX IV. Anticipated Adverse Events

(Acute) renal failure	Infection, systemic
(Aspiration) pneumonia	Inflammation
(Skin) laceration	Isolated ST segment elevation
(Vascular) bleeding	Liver toxicity
Acute Respiratory Distress Syndrome (ARDS)	Local Hematoma/ecchymosis
Air embolism	Localized skin reaction
Allergic reaction to contrast media	Mitral Insufficiency
Allergic skin reaction	Myocardial infarction with or without ST elevation
Altered Mental Status Confusion; Altered Level of Consciousness;	Nausea
Anaphylactic shock	Neurological disorders (poor coordination)
Anemia	Neurological disorders (tremor)
Anesthesia complications/reactions	Neuropraxia/Muscle contraction
Anoxic or hypoxic encephalopathy	Palpitations
Aortic Puncture	Papillary Muscle tear/injury
Apnea - sedation induced	Pericardial effusion resulting in tamponade
Arrhythmia (new or worsening of pre-existing arrhythmia)	Pericardial effusion without tamponade
Asthmatic attack	Pericarditis
Asymptomatic Cerebral Emboli	Periesophageal vagal nerve injury
Atelectasis	Peripheral nerve injury
Atrial fibrillation	Phlebitis
Atrial Septal Defect (acquired)	Phrenic nerve damage/injury
Atrio-Esophageal fistula	Pleural effusion
Auditory Disorder	Pneumothorax
AV fistula	Post- and perioperative pain
Back Pain	Post Procedural Hematuria
Bone disorder	Pseudoaneurysm
Bronchial fistula, Broncho-pericardium fistula	Pulmonary edema
Cardiac arrest	Pulmonary embolism
Cardiac pacemaker insertion or replacement	Pulmonary hypertension
Cardiac perforation	Pulmonary toxicity, like acute pulmonary syndrome
Cardiac Valve Rupture/Damage	Pulmonary vein dissection
Cardiogenic Shock	Pulmonary vein stenosis
Cerebro-Vascular accident (CVA)/Stroke	Renal Artery Stenosis
Chest pain/discomfort	Respiratory arrest
Complete or incomplete heart block	Respiratory depression

Conduction block	Respiratory failure
Coronary Artery Stenosis	Respiratory infection
Coronary artery thrombosis	Retinal Artery Embolism
Death	Retroperitoneal bleeding
Deep venous thrombosis	Rhabdomyolysis, including produced by body position or propofol
Diaphragmatic paralysis	Sedation induced CO_2 retention with lethargy and cholecystitis
Dislodgement/Malfunction of pacemaker/defibrillator leads	Seizure
Disseminated Intravascular Coagulation	Sepsis
Dizziness, presyncope, vertigo	Sinus bradycardia
Dysphagia	Sinus tachycardia
Dyspnea	Skin burn or necrosis
Endocarditis	Skin discoloration
Epigastric Distress	Skin edema
Epistaxis	Skin or soft tissue (radiation) injury/tear
Esophageal injury / perforation	Subclavian artery puncture
Expressive aphasia	Temperature elevation / Fever
Fatigue	Thrombocytopenia
Gastric hypomotility	Thromboembolism
Gastroesophageal reflux	Thrombosis
Gastrointestinal disorders	Thyroid disorders
Gastrointestinal diverticulosis	Toxic reaction
Gastroparesis	Transient extremity numbness
Headache	Transient Ischemic attack (TIA)
Heart failure (acute or chronic)	Urinary Retention Postoperative
Heart injury	Urinary tract injury or infection related to the urinary catheter
Heart valve insufficiency	Valvular damage/insufficiency
Hemoptysis	Vascular (access) dissection (including coronary arteries)
Hemorrhage	Vascular occlusion
Hemothorax	Vasovagal reactions
High/increased creatine phosphokinase (CPK)	Ventricular Fibrillation
Hypertension	Vessel damage/trauma
Hypervolemia	Vessel perforation
Hypotension	Vessel spasm (including coronary arteries)
Hypovolemia	Visual disturbance
Hypoxia	Worsening of pre-existing pulmonary disease
Increased phosphokinase level	Wound healing disturbance
Infection, localized	

*Atrial Fibrillation and exacerbation of an existing arrhythmia are anticipated adverse events. However, they will not be captured as such under this protocol, as they are considered recurrence of disease.