Clinical Evaluation of Intracardiac Ultrasound with the NUVISION™ NAV Ultrasound Catheter. "NUVISION NAV Study"

Protocol Number:	BWI202104
Sponsor:	Biosense Webster, Inc., a division of Johnson & Johnson with registered office at 31 Technology Drive, Suite 200 Irvine, CA 92618, USA
Operating Company:	Johnson & Johnson Medical NV/SA with registered office at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, represented by [redacted].
Funded by:	Biosense Webster, Inc., part of the Johnson & Johnson family of companies
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History of Changes:

Version — Date	Description
V 1.0 – 7 Nov 2022	Original Document
V 2.0 – 7 Apr 2023	Updated [redacted] Updated [redacted]

The NUVISION™ NAV Ultrasound Catheter and the NUVISION™ Connector Cable are approved and licensed in the USA but not yet approved in Europe and Israel, and thus considered investigational device for use in this study.

1. Table of Contents

2. List of Figures and Tables

3. List of Acronyms and Abbreviations

Acronym/ Abbreviation	Expanded Term
ACC	American College of Cardiology
ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial Fibrillation
ASIC	Application-Specific Integrated Circuit
AT	Atrial Tachycardia
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
CTA	Clinical Trial Agreement
CVA	Cerebrovascular Accident or Stroke
DD	Device Deficiency
EC	Ethics Committee
ECAS	European Cardiac Arrhythmia Society
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHRA	European Heart Rhythm Association
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
ESC	European Society of Cardiology
EtO	Ethylene Oxide
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration
F	French
FU	Follow-Up
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
HRS	Heart Rhythm Society
IB	Investigator's Brochure
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction for Use
LA	Left Atrium

Acronym/ Abbreviation	Expanded Term
LAA	Left Atrial Appendage
LAAO	Left Atrial Appendage Occlusion
LAT	Local Activation Time
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MDD	Medical Device Directive
MDR	Medical Device Regulation
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation
PI	Principal Investigator
PIU	Patient Interface Unit
PP	Per Protocol
PsAF	Persistent Atrial Fibrillation
PTCA	Percutaneous Transluminal Coronary Angioplasty
PV	Pulmonary Vein
PVCs	Premature Ventricular Complex
PVI	Pulmonary Vein Isolation
QC	Quality Control
RA	Right Atrium
RF	Radiofrequency
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOC	Standard Of Care
SPU	Signal Processing Unit
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TRUEref	Tightly Referenced Unipolar Electrode reference
TTM	TransTelephonic Monitor
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect
ULS	UltraSound
UM	User Manual
USADE	Unanticipated Serious Adverse Device Effect
VT	Ventricular Tachycardia

4. Key Roles and Responsible Parties

SPONSOR:

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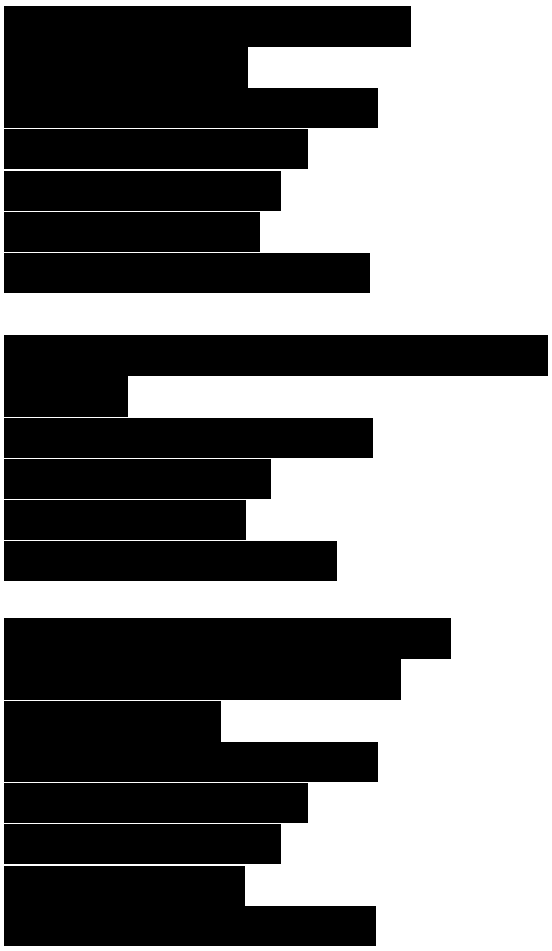
The Sponsor will finance the study, and a Clinical Trial Agreement (CTA) will manage the relationship between the sponsor, the investigator and the institution. Including but not limited to: description and acknowledgment of responsibilities, terms of collaboration, indemnification, requirements for payment, publication and intellectual property terms and guidelines for dispute resolution.

CONTACTS:



Whereas, the Clinical Study is sponsored by Biosense Webster Inc., Johnson and Johnson Medical NV/SA with registered offices at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, has been duly appointed by the Sponsor to conduct the Clinical Study on its behalf.

The sponsor maintains an updated list of Principal Investigators (PIs), the coordinating investigator (if appointed), address details of each investigational site, emergency contact details for the PIs at each site, roles and responsibilities and qualifications of each respective investigator, institutions and

Contract Research Organizations (if applicable). The definitive list shall be integrated into the study report.

The current protocol has been developed based on regulations applicable in Europe and Israel, for other countries outside Europe a country specific version of this study protocol may be developed, further defining regional regulations, if applicable.

5. Protocol Summary

Full Title	Clinical Evaluation of Intracardiac Ultrasound with the NUVISION™ NAV Ultrasound Catheter.
Short Title	NUVISION NAV Study
Protocol Number	BWI202104
Eudamed number	CIV-23-04-042835
Sponsor	Biosense Webster, Inc.
Indication	Intra-cardiac and intra-luminal visualization of cardiac and great vessel anatomy and physiology as well as visualization of other devices in the heart during cardiac interventional percutaneous procedures.
Description of Investigational Devices	The **investigational NUVISION™ NAV Ultrasound Catheter** (D-1426-01-SI), is a sterile, single use, disposable, diagnostic ultrasound imaging catheter designed for intracardiac use. It is built around the core design and technology of the existing NUVISION™ Ultrasound Catheter, 10 Fr (D-1423-01-S). [redacted] [redacted] The **investigational NUVISION™ Connector Cable** (FG10594) is used to connect the catheter to the GE Ultrasound System. The multipin SOUNDSTAR™ eco Cable is used to connect the catheter to the CARTO™ 3 System.
Premarket or Post market	Premarket
Study Design	Prospective, single arm, non-randomized, open-label, multi-center
Primary Objective	• Assess performance of the NUVISION™ NAV Ultrasound Catheter when used during study procedures

	• Assess safety of the NUVISION™ NAV Ultrasound Catheter when used during study procedures
Secondary Objective	• Characterize physician feedback regarding the deployment, maneuverability, navigational features and imaging quality acquired with the NUVISION™ NAV Ultrasound Catheter during study procedures
Primary Endpoints	• Performance: Completion of imaging required for the study procedure with the NUVISION™ NAV Ultrasound Catheter without resort to a non-study ultrasound device • Safety: Occurrence of serious adverse events within 7 days of index procedure related to the NUVISION™ NAV Ultrasound Catheter
Secondary Endpoints	• Physician assessment of deployment, maneuverability, navigational features and imaging quality acquired with the NUVISION™ NAV Ultrasound Catheter during the study procedures • Occurrence of all other serious adverse events within 7 days of index procedure (not related to the NUVISION™ NAV Ultrasound Catheter) • Occurrence of non-serious adverse events within 7 days of index procedure related to the NUVISION™ NAV Ultrasound Catheter
Study Population	Subjects who are scheduled to undergo an imaging process during an interventional cardiac ablation procedure for management of the following: 1) Scar-related Atrial Tachycardia (AT; includes atypical atrial flutter), procedures resulting from previous atrial fibrillation ablation; 2) Persistent Atrial Fibrillation (PsAF); 3) Paroxysmal Atrial Fibrillation (PAF); 4) Ventricular Tachycardia (VT): ischemic and non-ischemic VT, cardiomyopathy and idiopathic VT; 5) Premature Ventricular Complex (PVC);
Sample Size	Up to 30 subjects will be enrolled in the study.
Geographic areas to be included	Europe and Israel
Study Duration	Approximately 5 months enrollment and 7-day follow-up per subject.
Visit Intervals	Baseline/procedure, 7-day follow-up phone call or clinic visit after study procedure
Procedure(s) description	During study procedures, investigators will use the investigational catheter instead of the institution's standard ultrasound catheter (e.g. SOUNDSTAR™ ultrasound catheter).

	The use of the investigational catheter is mandatory for thrombus detection, imaging for volume measurements, during transseptal puncture and as navigational ultrasound (ULS) catheter throughout the procedure. Any use of a non-investigational ultrasound device will be considered a failure of the primary effectiveness endpoint.
Statistical Analysis	There will be no formal hypothesis testing on outcomes in this study. The safety and performance data below will be summarized with descriptive statistics. Analysis for these endpoints will be performed overall and per procedure type (atrial ablation/ventricular ablation). **<u>Analysis for Primary Endpoints:</u>** **Performance** - The number and proportion of subjects in whom imaging is performed successfully with the investigational catheter without resort to a non-study ultrasound device. **Safety** - Serious Adverse Events related to the investigational catheter during the 7-day follow-up period **<u>Analysis for Secondary and Additional Endpoints:</u>** **Physician Feedback** - Physician feedback on the catheter deployment, maneuverability, navigational features and imaging quality acquired with the investigational catheter will be collected and summarized by using a physician-completed survey with a Likert scale of 1 to 7 (1=poor and 7=excellent). **Procedural data, including, but not limited to:** - Anatomical structures assessed - Whether imaging for Left Atrium (LA) and Left Ventricle (LV) volume measurements was done - Total fluoroscopy time - Total procedure duration **Safety** - All other SAEs during the 7-day follow-up period (not related to the investigational catheter) - All investigational catheter related non-serious Adverse Events during the 7-day follow-up period
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for participation in this clinical investigation.

	1. Diagnosed with and candidate for clinically-indicated cardiac ablation procedure for the management of ventricular tachycardia, premature ventricular complex, scar-related atrial tachycardia or atrial fibrillation (patients having undergone a previous ablation procedure may be included). 2. Age 18 years or older. 3. Signed Patient Informed Consent Form (ICF). 4. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.
Exclusion Criteria	Subjects who meet any of the following exclusion criteria are not eligible for enrollment. 1. Structural heart defect which can only be repaired by cardiac surgery 2. Pericarditis within 6 months 3. LVEF ≤ 25% for VT patients 4. LVEF ≤ 40% for patients with atrial arrhythmia 5. History of chronic gastro-intestinal medical problems involving the esophagus, stomach and/or untreated acid reflux 6. History of abnormal bleeding and/or clotting disorder. 7. Clinically significant infection or sepsis 8. History of stroke or TIA within the past 6 months of enrollment 9. Uncontrolled heart failure or NYHA function class IV 10. Implanted with a pacemaker or intracardiac cardiac defibrillator within the past 6 weeks (42 days) 11. Implanted with a mechanical valve 12. Diagnosed atrial or ventricular myxoma, interatrial baffle or patch, tumor or other abnormality that precludes catheter introduction or manipulation. 13. Any of the following within 6 months (182 days) of enrollment a. Major surgery except for the index procedure b. Myocardial infarction c. Unstable angina d. Percutaneous coronary intervention (e.g. CABG or PTCA) 14. Patients with any other significant uncontrolled or unstable medical condition (such as uncontrolled bradyarrhythmia's, ventricular arrhythmias, hyperthyroidism, or significant coagulation disorder) 15. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study. 16. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation. 17. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being. 18. Concurrent enrollment in an investigational study evaluating another device or drug.
Time and Events Schedule	**<u>Pre-Procedure/Baseline</u>** • Informed consent documentation • Demographics • Medical history assessment

	• Transthoracic echocardiogram for assessment of ejection fraction (not required if the subject has undergone an imaging procedure within the last 6-months where the requested values were assessed) • Cardiac computed tomography (CT) for assessment of cardiac anatomy (not required if the subject has undergone a CARTOMERGE™ compatible cardiac CT within 60 days of the procedure) • Pregnancy test for women of child-bearing potential (within 1-week before the procedure) • Adverse events **Procedure** • Use of the NUVISION™ NAV Ultrasound Catheter to confirm absence of thrombus • Procedural parameters • Use of the NUVISION™ NAV Ultrasound Catheter 1. Imaging for LA and LV volume measurements 2. During transseptal puncture 3. Navigational feature throughout the procedure • Adverse events and procedural complications • Device deficiency • Physician survey **Discharge** • Adverse events **7-Day Follow-Up visit** • Adverse events

Assessments[1]	Screening / Baseline (Clinic Visit)	Study Procedure	Discharge	7-day Follow-up (Clinic Visit or Phone call)
Informed Consent[2]	✓			
Demographics	✓			
Medical and Cardiac History[3]	✓			
Transthoracic Echo (TTE)[4, 8]	✓			
Cardiac CT[5, 8]	✓			
Pregnancy Test[6, 8]	✓			
Thrombus detection[7]		✓		
Adverse Events[9]	✓	✓	✓	✓

1. Standard of care assessments can be performed before ICF signature
2. Informed consent to be signed **within the 60 days prior to procedure**
3. Medical history-including but not limited to arrhythmia, heart disease and thromboembolic events
4. TTE to determine the LVEF % **within the 60 days prior to procedure** (if the subject has undergone imaging in the last 6 months where the requested values were assessed, the assessment is not required)
5. Cardiac CT for assessment of cardiac anatomy **within 7 days prior to procedure** (if the subject has undergone a CARTOMERGE™ compatible CT within 60 days of the procedure, the assessment is not required)
6. Pregnancy tests for women of child-bearing potential only **within the 7 days prior to procedure**
7. Thrombus detection, to rule out the presence of thrombus – **mandatory to be performed with the investigational catheter during the study procedure**
8. Assessment should not be repeated for the study if already done per standard of care within the protocol defined time limits.
9. AEs must be collected from the time the subject signs the informed consent onward.

6. Background Information and Scientific Rationale

6.1 Background Information

Intracardiac Echocardiography (ICE) is a common imaging modality used to visualize the various heart chambers during percutaneous interventional and electrophysiological procedures. For years, two-dimensional (2D) ICE was a widely used imaging technology in the electrophysiology (EP) and catheterization labs as alternative for Transesophageal Echocardiography (2D and real time (RT) 3D TEE) in both adults and children [1, 2, 3, 4, 5, 6].
Recently, ICE has moved from 2D echo to 3D and 4D echo imaging capabilities, with 4D being high-quality 3D moving images. This has greatly improved device guidance visualization and allows real-time assessment of cardiac anatomy [7, 8]. The usage of ICE imaging is now also increasing for Left Atrial Appendage Occlusion (LAAO) procedures for which TEE imaging was the gold standard [9, 10]. Various articles have been published demonstrating that ICE catheters can help physicians to guide and localize devices in the heart, guide transseptal puncture, LAAO and ablation procedures and, can be used as an adjunct with other imaging modalities such as fluoroscopy to aid in placement of devices. ICE can also be used to exclude procedural complications such as a pericardial effusion or thrombus formation [10, 11, 12, 13].

The introduction of the 4D NUVISION™ ICE Catheter Into the interventional cardiology and cardiac electrophysiology segments was successful and the product is routinely used by leading centers in the US.
The First-in-Human Experience With Novel 4D ICE Catheter For Catheter Ablation and Left Atrial Appendage (LAA) Closure Procedures- HRS 2021 late-breaking study shows the utility of 3D/4D intracardiac echo image guidance for EP procedures [14].

This study will focus on a Navigational 4D ICE Ultrasound Catheter NUVISION™ NAV developed by Biosense Webster including the CARTO™ 3 interface which will enable electrophysiologists, structural heart cardiologists, and other physicians to image the heart on the CARTO™ 3 mapping windows in conjunction with other navigational devices for diagnostic, device placement guidance and mapping.

The NUVISION™ NAV Ultrasound Catheter is a single use, disposable, diagnostic ultrasound imaging catheter designed for intracardiac echo use. It is built around the core design and technology of the existing NUVISION™ ICE Catheter, 10 Fr (D-1423-01-SI) and will integrate the handling, mechanical performance, and imaging capability of his predecessor the NUVISION ICE catheter. [redacted]

Those features will support electrophysiologists in intra-cardiac and intra-luminal visualization of cardiac and great vessel anatomy and physiology as well as visualization of other devices in the heart. The catheter is intended for imaging guidance only, not treatment delivery, during cardiac interventional percutaneous procedures.

[redacted]

- [redacted]

6.2 Previous Experience with the Investigational Catheter

6.2.1 Investigational catheter animal testing

This study is the first in human study with the investigational catheter. Refer to the Investigator's Brochure (IB) for a detailed description of the preclinical testing performed.

[redacted]

[redacted]

6.3 Rationale for Design of the Clinical Investigation

The study is a first in human study with the investigational catheter. Clinical experience in 30 subjects, in various chambers of the heart, operated by multiple physicians in different hospitals will allow for initial characterization of the performance and safety of the investigational catheter. The selected physicians have experience with similar products and/or pre-clinical experience with the investigational catheter.

Further knowledge regarding the performance and safety of the investigational catheter will be gathered during the External Evaluation in the US (FDA 510(k) clearance received on 16-Feb-2023).

The sample size was selected based on previous experience with similar design in first in human assessments of diagnostic catheters. This study is meant to characterize the catheter's ability to perform safely in various types of procedures. No clinical claims of effectiveness or patient outcomes will be made from this study.

Therefore, the study is designed as a prospective, multicenter, single arm clinical study. Only descriptive analysis will be performed.

6.4 Potential Risk and Benefit

6.4.1 Known Potential Risks

The identified potential risks and hazards are common to the use of Intracardiac Echocardiography (ICE) catheters during cardiac mapping and ablation procedures:

- **Arrhythmia**: The possible arrhythmia associated with the use of ICE catheters (risk is <0.2%) could occur by manipulation in unintended locations, or locations of high probability for arrhythmia such as atrial appendages or ventricular walls.

  The added CARTOSOUND™ sensor in this catheter will allow easier catheter orientation and location identification, what is expected to assist the operator in avoiding arrhythmogenic regions of the heart.

- **Heart injury** (heart injury, cardiac perforation)**:** Heart injury may result from catheter

manipulation when appropriate visualization is unavailable (risk is ≤0.002%). Cardiac perforation may result in pericardial effusion or cardiac tamponade which requires percutaneous pericardial drainage or surgical repair [15]. To prevent heart injury, the investigational catheter should be used as instructed.

The CARTOSOUND™ capability allows the operator to map the intended region/chamber without physically entering the chamber with the catheter. This will reduce catheter manipulation and avoid regions of the heart susceptible to injury.

- **Burn**: as for all electrical equipment, improper use and/or defects may lead to a short circuit, leading to skin burns (risk <0.02%).
- **Chest injury** (esophageal injury): this catheter is contraindicated for use as TEE. When used as TEE esophageal injury may occur (risk ≤0.002%)
- **Thromboembolism or embolus**: Intracardiac ultrasound catheters are not irrigated, a thrombus could form (risk ≤0.002%). Embolization of thrombus could produce stroke, myocardial infarction, or other ischemic injury. To prevent this injury, The Activated Clotting Time (ACT) should be maintained above the minimum level of 300 seconds while the investigational catheter is in the heart.
- **Hypersensitivity** (allergic reaction, anaphylactic reaction): to the local anesthetic, sedatives, X-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%) [16, 17, 18, 19, 20].
- **Infection** (sepsis, wound infection): The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%) [21, 22]. This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.
- **Arterial or venous injury**: including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk < 1%) [21, 22]. These types of injuries may cause hemorrhage, hematoma, or ischemic injury to an extremity or major organ. Hemorrhage as a result of anticoagulation (risk < 0.5%), which may require transfusion [21, 22]. This risk can be minimized by using clinical standards of care, and a compatible sheath.
- **Entanglement and/or entrapment**: When the investigational catheter is within the proximity of the tricuspid valve or mitral valve, caution needs to be applied to avoid entanglement and/or entrapment in cardiac tissue or vascular structure (risk <0.02%) [23].
- **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%) [17, 21, 22, 24, 25, 26, 27, 28].

A Comprehensive List of Anticipated Adverse Events for standard cardiac RF ablation procedures can be found in chapter 15.2.4, table 6

There are no anticipated potential direct risks to the patient related to the investigational connection cable.

6.4.2 Minimization of Risk

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.

Patient selection: Subjects will be prescreened carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to exclude subjects with a medical history or condition that increases their risk of adverse events (refer to Section 9.2 for the Exclusion Criteria).

Imaging for thrombus detection: Subjects will be screened for the presence of thrombus with the investigational ultrasound catheter, which is intended to decrease the potential for thromboembolic complications.

Within procedure safeguards: Investigators highly skilled in intracardiac mapping and ablation procedures will be selected for participation in the study. These procedures will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. Study investigators will undergo training prior to performing procedures with the investigational catheter.

Post-procedural management: Investigators will be encouraged to follow recommended guidelines for systemic oral anticoagulation therapy for a given subject after their procedure.

Safety data during enrollment and follow-up will be closely monitored and evaluated per the specific safety management plan for the study. Also, refer to "Assessment of Safety" in section 15.0 for more information on safety management.

6.4.3 Anticipated Clinical Benefits

For ablation procedures, the investigational devices (catheter and connection cable) are expected to contribute to the improvement of workflow and procedural efficiency by:

- Supporting real-time 2D, 3D and 4D ultrasound imaging options controlled by user as well as pulsed and continuous wave color flow doppler in each imaging mode.
- Allowing customized ultrasound image preparation and presentation to suit user clinical needs.
- Combining ultrasound imaging with the CARTO™ 3 Navigation System to provide accurate magnetic navigation for electro-anatomical mapping and better image quality.
- Having the ability to visualize internal cardiac structures in real time in conjunction with static cardiac CARTO maps.
- Minimizing fluoroscopy usage (reduced fluoroscopy dose and time) which reduces the radiation exposure.

The potential effectiveness and efficiency gains stated above are expected to provide benefit to patients by shorter procedure times and better clinical outcomes.

7. Objectives and Purpose

7.1 Objective

The primary objective of this study is to assess the performance and safety of using the investigational catheter.

A secondary objective is to gather physician assessment of deployment, maneuverability, navigational features and imaging quality acquired with the investigational catheter.

7.2 Purpose

The purpose of this study is to evaluate the safety and feasibility of the NUVISION™ NAV Ultrasound Catheter performance for further product development.

8. Study Design and Endpoints

8.1 Description of the Study Design

This study is a prospective, single arm, non-randomized, open-label, multi-center study. Up to 30 subjects will be enrolled.

Subjects meeting the inclusion / exclusion criteria and who sign the informed consent form (ICF) will be enrolled in this study. The clinical investigation is targeting approximately 4 sites in Europe and Israel.

This study will serve to characterize the performance and safety of using the investigational catheter in procedures for subjects in up to five different subgroups (scar-related AT, PsAF, PAF, VT and PVC). Subjects will be treated per investigator's standard of care and followed until 7 days post-procedure.

Planned analyses are described in the Statistical Analysis section 20.0 of this clinical investigational plan.

8.2 Study Endpoints

8.2.1 Primary Endpoints

Performance
Completion of imaging required for the study procedure with the NUVISION™ NAV Ultrasound Catheter without resort to a non-study ultrasound device.

Safety
Occurrence of serious adverse events within 7 days of index procedure related to the NUVISION™ NAV Ultrasound Catheter.

8.2.2 Secondary Endpoints

Physician feedback
Physician assessment of deployment, maneuverability, navigational features and imaging quality acquired with the NUVISION™ NAV Ultrasound Catheter during the study procedures.

Safety
- Occurrence of all other serious adverse events within 7 days of index procedure (excluding NUVISION™ NAV Ultrasound Catheter related SAE's)
- Occurrence of non-serious adverse events within 7 days of index procedure related to the NUVISION™ NAV Ultrasound Catheter

8.4.3 Additional Endpoints

- Additional procedural data, including but not limited to:
  - Anatomical structures assessed

- Whether imaging for Left Atrium (LA) and Left Ventricle (LV) volume measurements was done
- Total fluoroscopy time
- Total procedure duration.

– Additional safety data
All non-serious adverse events not related to investigational catheter.

9. Study Population

The study population consists of subjects scheduled to undergo an imaging process for an interventional cardiac ablation procedure for management of the following:

1) Scar-related Atrial Tachycardia (AT; includes atypical atrial flutter), procedures resulting from previous atrial fibrillation ablation;
2) Persistent Atrial Fibrillation (PsAF);
3) Paroxysmal Atrial Fibrillation (PAF).
4) Ventricular Tachycardia (VT): ischemic and non-ischemic VT, cardiomyopathy and idiopathic VT.
5) Premature Ventricular Complex (PVC)

9.1 Participant Inclusion Criteria

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

1. Diagnosed with and candidate for clinically-indicated cardiac ablation procedure for the management of ventricular tachycardia, premature ventricular complex, scar-related atrial tachycardia or atrial fibrillation (patients having undergone a previous ablation procedure may be included).
2. Age 18 years or older.
3. Signed Patient Informed Consent Form (ICF).
4. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

9.2 Participant Exclusion Criteria

Candidates will be excluded if ANY of the following criteria apply:

1. Structural heart defect which can only be repaired by cardiac surgery
2. Pericarditis within 6 months
3. LVEF ≤ 25% for VT patients
4. LVEF ≤ 40% for patients with atrial arrhythmia
5. History of chronic gastro-intestinal medical problems involving the esophagus, stomach and/or untreated acid reflux
6. History of abnormal bleeding and/or clotting disorder.
7. Clinically significant infection or sepsis
8. History of stroke or TIA within the past 6 months of enrollment
9. Uncontrolled heart failure or NYHA function class IV
10. Implanted with a pacemaker or intracardiac cardiac defibrillator within the past 6 weeks (42 days)
11. Implanted with a mechanical valve
12. Diagnosed atrial or ventricular myxoma, interatrial baffle or patch, tumor or other abnormality that precludes catheter introduction or manipulation.

13. Any of the following within 6 months of enrollment
    a) Major surgery except for the index procedure
    b) Myocardial infarction
    c) Unstable angina
    d) Percutaneous coronary intervention (e.g. CABG or PTCA)
14. Patients with any other significant uncontrolled or unstable medical condition (such as uncontrolled bradyarrhythmia's, ventricular arrhythmias, hyperthyroidism, or significant coagulation disorder)
15. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
16. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation.
17. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being.
18. Concurrent enrollment in an investigational study evaluating another device or drug.

10. Participant Withdrawal or Termination

10.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request without penalty or loss of benefits to which they may otherwise be entitled. Participants will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason without prejudice to their future medical care by a physician or the institution.

An investigator may terminate a subject's participation in the study if:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Withdrawal is in the subjects' best interest
- Subject withdraws consent
- Subject is lost to follow-up

Every subject should be encouraged to remain in the study until they have completed the protocol required follow-up period.

10.2 Handling of Participant Withdrawals or Termination

If a subject is removed or withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic Case Report Form (eCRF). If the subject withdraws consent PRIOR to insertion of the study catheter, the subject can be replaced. If the subject is withdrawn due to an AE or SAE, the Investigator should follow the subject until the AE/SAE has resolved or is considered stable or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

If a subject is unable to return for an office/clinic visit or cannot 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, then the subject will be considered "lost to follow-up" for the study.

Subjects who have signed the ICF, but are later found not to be eligible PRIOR to insertion of the study catheter can be replaced. Replacement subjects will be recruited and enrolled following the same procedures as non-replacement subjects.

All applicable case report forms up to the point of subject withdrawal must be completed. Data collected up to the point of subject withdrawal may be used, unless local regulations apply.

10.3 Subject Disposition

- **Enrolled Subjects:** Patients who sign the ICF.
- **Excluded Subjects:** Subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will be subjected to safety event reporting between ICF signature and date of exclusion. Subjects who signed the ICF but are found to be ineligible prior to insertion of the catheter are also considered as excluded.
- **Discontinued Subjects**: Enrolled subjects who have the study catheter inserted but no assessments are performed with it. Discontinued subjects will remain in follow-up for 7 days for safety evaluation.
- **Lost to Follow-up Subjects:** Enrolled subjects of which contact is lost after most recent visit (despite 3 documented attempts to contact the subject).
- **Withdrawn / Early Termination Subjects:** Subjects who withdraw consent for study participation or are withdrawn by the investigator, are terminated from the study 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 from the study prior to the final study visit.

11. Responsibilities

11.1 Investigator Responsibilities

Investigators at each participating clinical site will have the following responsibilities:

- Assuring compliance by site personnel with the provisions of the protocol
- Providing the Sponsor with:
  - Signed, dated Investigator Agreement
  - Written Ethics Committee (EC) approval letters and EC-approved consent forms
  - Signed, dated Financial Disclosure form for each participating investigator
  - Curriculum vitae for each investigator
- Maintain an accurate and current Delegation of Authority log which identifies individuals authorized to perform work for the study and assuring compliance by site personnel with the provisions of the protocol
- Completing the appropriate training on the device and the Clinical Study Protocol/ Investigational Plan prior to enrolling and using the catheter in subjects
- Maintain accurate and current logs for the study such as:
  - Subject log, Device Accountability Log

- Obtain initial and amendment (if applicable) EC approval and annual review/approval thereafter for the study protocol and informed consent as applicable
- Obtain ICF and enroll patients
- Perform medical procedures
- Order tests required by the study protocol
- Follow subjects until the end of the study protocol
- Accurately complete and sign eCRFs in a timely manner
- Maintain relevant source documentation and allow Sponsor direct access to perform monitoring or auditing duties
- Maintain records and provide reports according to prevailing regulatory requirements
- Share relevant study-related information with delegated study staff
- Inform the appropriate entities (e.g., Sponsor, Competent Authority (CA), EC) in a timely manner regarding the occurrence of AEs and/or product malfunctions.
- Making sufficient effort to maintain contact with treated subjects who fail to comply with the follow-up requirements
- Maintain study records for at least 10 years or as specified per country specific record retention requirements after the study is completed and or terminated. The Sponsor will notify the Investigator of either of these events.
- Complying with EC and Sponsor annual report requirements, including the final report.

11.2 Sponsor Responsibilities

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

- Conduct of pre-study site assessment and approval
- Preparation and modification (if applicable) of study documents including but not limited to the Clinical Study Protocol/Investigational Plan, CRFs and informed consent
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Conduct protocol and device training for investigators and research personnel as applicable
- Set-up of study-specific committees (if applicable).
- Obtain signed study contracts from investigators/hospitals, Clinical Research Organizations (CROs) and other involved parties
- Ship study devices to each site
- Monitor sites for the duration of the study
- Maintain study database
- Inform investigator of his/her responsibilities
- Submit and obtain approval for study from applicable regulatory agencies
- Preparation of reports summarizing the status of the study no less than annually. These reports will be supplied to the PI at each site.
- Update Report of Priors, IFU, IB, and Risk Analyses, as applicable
- Update investigators on safety issues, if needed

- Report (including AE's and DDs) to study investigators and regulatory agencies, as required
- Have relevant safety information reviewed by the Study Safety Lead, as required
- Communications with the CA
- Submission of any amendments to the Clinical Study Protocol/Investigational Plan to the CA.
- Maintain study records for at least 10 years or as specified per country specific record retention requirements after the study is completed and or terminated.

12. Study Device Description

12.1 Device Acquisition

After obtaining a fully executed clinical trial agreement and appropriate approvals, the sponsor will initiate shipment(s) of investigational devices to the site. The Sponsor will keep records of all investigational devices shipped to the site. Approved investigational devices will be shipped directly to the site and will be received by the site. Investigators are responsible for appropriate logging of the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), date and identity that each device was used in the study, disposition information regarding disposal or return to the Sponsor.

12.2 Device Storage and Stability

Devices are to be stored in a secure/locked location and in accordance with the catheter and cable IFU. Do not use the (disposable) devices after the "Use By" date.

12.3 Device Preparation

Information related to device preparation can be found in the IFU.

12.4 Instructions for Use

A comprehensive set of IFU for the study devices and all accessory cables/interface cables is contained in each product package and is also available upon request.

12.5 Device Description and Specific Considerations

The investigational study devices are indicated in Figure 1.

[redacted]

12.6 Additional Equipment

12.6.1 System Components and Setup

[redacted]

The following devices, which may be CE marked by other companies, may also be required for the procedure:

[redacted]

Figure 2: Connectivity diagram for system set-up

[redacted]

[redacted]

12.6.2 Required Study Devices

These devices must be used for the study procedure and are required per protocol.

Table 1: Required Study Devices

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

13. Study Medication

Medications in this protocol are at physician discretion and should reflect the center's standard of care for the procedure type. Anticoagulation therapy should be administered at a dose sufficient to meet a minimum ACT level of 300 seconds prior to insertion of the investigational catheter and throughout the procedure.

14. Study Schedule

14.1 Screening and Informed Consent

Candidates presenting to the institution with a cardiac arrhythmia in scope of the protocol, and considered for an ablation procedure, should be screened by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion

criteria. Sites will be instructed to screen all subjects who require a documented ablation procedure for a cardiac arrhythmia in scope of the protocol, without regard to sex or race.

The study investigator or designated member of the research team will obtain written informed consent from the subject. The patient informed consent procedure must be done within 60 days before the actual study procedure takes place. The background of the proposed study and the potential benefits and risks of the study should be explained to the subject. The subject or legal representative must sign the consent form prior to any study-specific exams or tests are provided to them that fall outside of the standard of care. The consent form used must have prior approval from the CAs and study site's EC. Failure to obtain informed consent renders the subject ineligible for participation in the study.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with International Conference on Harmonization-Good Clinical Practices (ICH-GCP) and with applicable local and national regulations. If new information becomes available that can significantly affect a subject's future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by, dating and signing an amended ICF.

Each subject screened for enrollment in the clinical investigation who signs the patient ICF will be enrolled into the study. No subject should undergo any clinical investigation specific tests or examinations that fall outside the standard of care without first signing the patient ICF for this clinical investigation.

14.2 Baseline Evaluation and Procedures

14.2.1 Pre-Procedure/Baseline Assessments

Below pre-procedure assessments and data collection must be performed prior to the ablation procedure.

Within 60 days prior to the study procedure:

- **Baseline Medical, Cardiac History** (including findings from TTM, ECG, Holter monitor, etc.)
- **Transthoracic Echocardiogram (TTE) –** imaging to assess ejection fraction
  Note: Available imaging within 6 months prior to the procedure (TTE or other acceptable equivalent cardiac imaging – i.e. CT/MRI) can be used to assess the LVEF. In case the imaging assessment is older than 6 months LVEF shall be re-assessed prior to insertion of the study catheter. In case the re-measurements before study catheter insertion fail to meet the LVEF criteria, the subject will be considered as not meeting eligibility and will be excluded.

Within 7 days prior to the study procedure:

Cardiac CT – imaging to assess the cardiac anatomy*Note: An available Cardiac CT, obtained within 60 days prior to the procedure, with a segmentable LA and LV compatible with CARTOMERGE™ can be used as reference when analyzing the CARTO™ and GE Vivid™ S70N data. In case the CT data is older than 60 days, or not compatible with CARTOMERGE™, a new CT should be obtained prior to the start of the study procedure.*

- **Pregnancy Test –** only performed on women of child-bearing potential

All adverse events observed/reported after enrollment (ICF signed) should be collected and reported to the sponsor and ethics committee, as appropriate.

14.2.2 Study Procedure

Subjects will arrive to the electrophysiology laboratory for their study procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator)

Overall Use of the Investigational Device

During study procedures, investigators will use the investigational catheter instead of the institution's standard ultrasound catheter choice (e.g. SOUNDSTAR™). Any use of a non-investigational ultrasound device will be considered a failure of the primary performance endpoint.

The use of the investigational NUVISION™ NAV Ultrasound Catheter is **mandatory** for:

- Thrombus detection and LA/LV imaging for volume measurement at the start of the procedure;
- During transseptal puncture;
- And as navigational ULS catheter throughout the procedure.

Imaging guidance for LA/LV volume measurements:

- Capture preferably the full chamber in one ULS volumetric segment, if needed several segments can be taken.
- For capturing of the LA:
  - Capture 4D ULS clip (full 90°x90°) of the LA (with PVs and LAA) taken from the RA.
  - Repeat the acquisition from 3-6 slightly different positions, where the LA volume is partial.
    Note: Capture 4D ULS clip before transseptal and insertion of any other catheters to the LA, by using the default ULS settings, and without using the "zoom" function.
  - Place the investigational NUVISION™ NAV Ultrasound Catheter near the interatrial septum and make sure to capture the ENTIRE left atrium.
  - Confirm by seeing both anterior-posterior and Roof to Mitral valve planes.
  - Make sure to allow sufficient ULS depth by visualizing the distal LAA.
- For capturing of the LV:
  - The catheter can be positioned either in the RA near the inferior septum or in the right ventricle (RV) near the interventricular septum.
  - Make sure to allow sufficient ULS depth by visualizing the entire chamber from the Mitral valve to the distal apex.

Investigators should use the CARTO™ 3 system to **"bookmark"** instances of abnormal study catheter "imaging noises". This will allow for further analysis of the data.

Standard of Care Ablation Procedure

Treatment will be per institution's standard of care (SOC).

14.2.3 Collection of Procedure Data for Post-Analysis (non-SOC)

At the completion of the study procedure, two back-up copies of the CARTO™ 3 and GE Vivid™ S70N Ultrasound Console system files will be made. One copy should be kept at the site within the investigator site or patient binders, and one anonymized copy will be provided to/collected by the Sponsor. Also, an anonymized copy of cardiac CT images will be collected to be used as reference when analyzing the CARTO™ and GE Vivid™ S70N data.

14.2.4 Data Collection during Study Ablation Procedure

Procedural parameters collected during the procedure include but are not limited to:

- Anatomical structures assessed
- Imaging for Left Atrium (LA) and Left Ventricle (LV) volume measurements
- Total fluoroscopy time
- Total procedure duration.

Following each procedure, physician feedback on the investigational catheter and associated software used will be collected, using a 7-point Likert-scale survey; it will include feedback on deployment, maneuverability, navigational features and imaging quality acquired. The survey will be entered into the eCRF for analysis.

14.2.5 Pre-Discharge Assessments

Once the investigator has achieved desired treatment results, the subject will be monitored as per the institution standard of care (post procedure practice) and subject will be discharged from the hospital in accordance with the hospitals standard procedures.

Before hospital discharge, any adverse events that have occurred since the procedure should be documented, entered into the eCRF, and reported, as appropriate.

14.3 Post-procedure Follow-up Schedule

All subjects will be contacted 7-days post-procedure via telephone call or by attending a clinic visit to assess for any adverse events. The window for this remote or in-clinic visit is +2 days (7-9 days). Alternative contact methods are allowed in case a telephone call or clinic visit is not feasible (*e.g.* telemedicine or mail contact). The method of contact should be documented in the eCRF.

At the 7-day follow-up visit, the following assessment will be performed:

- Adverse events (from the time of the procedure up until the visit)

14.4 Early Termination Visit

If early termination of the study is required due to safety concerns, each site will undergo a monitoring visit 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. Any enrolled subject will continue to be followed per the study protocol requirements. In case

of early termination due to safety concerns, reporting to EC and CA may be required per local regulations.

14.5 Unscheduled Visit

If a subject returns for a potential study related cardiovascular visit outside of the protocol-defined visit schedule provided in table 2, the visit will be considered "unscheduled" (UNS). An investigator may request an unscheduled visit in the presence of a new or worsened cardiovascular condition. For this study, unscheduled visits are recorded in the eCRF linked to the next scheduled study visit per clinical investigational plan.

14.6 Core Laboratory for Evaluation

No core labs will be used for this study.

14.7 Schedule of Events Table

Table 2 displays the required schedule for subject treatments and evaluations.

Table 2: Summary of Subject Visits and Assessments

Assessments[1]	**Screening / Baseline** (Clinic Visit)	**Study Procedure**	**Discharge**	**7-day Follow-up** (Clinic Visit or Phone call)
Informed Consent[2]	✓			
Demographics	✓			
Medical and Cardiac History[3]	✓			
Transthoracic Echo (TTE)[4,8]	✓			
Cardiac CT [5,8]	✓			
Pregnancy Test[6,8]	✓			
Thrombus detection[7]		✓		
Adverse Events[9]	✓	✓	✓	✓

1. Standard of care assessments can be performed before ICF signature
2. Informed consent to be signed **within the 60 days prior to procedure**
3. Medical history-including but not limited to arrhythmia, heart disease and thromboembolic events
4. TTE to determine the LVEF % **within the 60 days prior to procedure** (if the subject has undergone imaging in the last 6 months where the requested values were assessed, the assessment is not required)
5. Cardiac CT for assessment of cardiac anatomy within 7 days prior to procedure (if the subject has undergone a CARTOMERGE™ compatible CT within 60 days of the procedure, the assessment is not required)
6. Pregnancy tests for women of child-bearing potential only **within the 7 days prior to procedure**
7. Thrombus detection, to rule out the presence of thrombus – **mandatory to be performed with the investigational catheter during the study procedure**
8. Assessment should not be repeated for the study if already done per standard of care within the protocol defined time limits.
9. AEs must be collected from the time the subject signs the informed consent onward.

15. Assessment of Safety

15.1 Specific Safety Parameters

15.1.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a subject whether or not related to the investigational device.

Specifically, an AE is **any** undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the investigational device or procedure. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline are considered AEs.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Such conditions should be added to background medical history, if not previously reported. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Arrhythmia recurrence by itself is considered a recurrence of disease (pre-existing condition), and, therefore, **does not meet the definition of an AE**.

15.1.2 Definition of Serious Adverse Event (SAE)

A SAE is any event that meets one or more of the following criteria:

- Leads to death
- Leads to a serious deterioration in the health of a subject that resulted in:
  - A life-threatening illness or injury
  - An injury or permanent impairment of a body structure or a body function
  - In-patient hospitalization or prolongation of an existing hospitalization*
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
  - Chronic disease
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

*Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE. An AE would meet the criterion of "hospitalization" if the event necessitated an admission to a health care facility (e.g., 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.

15.1.3 Adverse Device Effect / Serious Adverse Device Effect

An adverse device effect is an AE related to the use of the investigational medical device.

NOTE 1- This includes any AE resulting from insufficiencies or inadequacies in the IFU, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

15.1.4 Unanticipated (Serious) Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) or Unanticipated Serious Adverse Device Effect (USADE) is any SAE on health, safety, any life-threatening problem, or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of occurrence in the investigational plan or risk analysis report, or any other unanticipated serious problem associated with a device that relates to rights, safety, or welfare of subjects. Refer to table 6 for a comprehensive list of foreseeable and anticipated AEs.

15.1.5 Study Device Deficiency

A device deficiency means any inadequacy in the identity, quality, durability, reliability, usability, safety or performance, including of an investigational device, including

- Malfunction (failure to perform in accordance to its intended purpose when used in accordance with the IFU/Clinical Investigational Plan (CIP)/IB),
- Use errors,
- Inadequacy in information supplied by the manufacturer.

If a device failure is detected or suspected, it should be documented on the appropriate eCRF and device failure and AE must be reported per section 0 AE documentation and reporting requirements.

15.2 Classification of an Adverse Event

15.2.1 Severity of Event

The intensity or severity of each AE must be assessed according to the following classifications:

Table 3: Intensity or Severity Definitions

Mild	Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

15.2.2 Relationship to Study Device

For all collected AEs, the clinician who examines and evaluates the participant will determine the AEs causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below as described per Medical Device Regulation (MDR)

Table 4: 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 be reasonably explained by another cause, but additional information may be obtained
	Possibly	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible
	Not related	Relationship to the investigational device can be excluded
Study Procedure	Definitely (Causal Relationship)	The event is associated with the study procedure beyond reasonable doubt
	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
	Possibly	The relationship with the study procedure is weak but cannot be ruled out completely. Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible
	Not related	Relationship to the procedure can be excluded

15.2.3 Outcome

The outcome of each AE must be assessed according to the following classifications:

Table 5: Adverse Event Outcome Classifications

Classification		Definition
Resolved without sequelae		Subject fully recovered with no observable residual effects
Resolved with sequelae		Subject recovered with observable residual effects
Ongoing	**Improved**	Subject's condition improved, but residual effects remain
	Unchanged	AE is ongoing without changes in the overall condition
	Worsened	Subject's overall condition worsened
Death		Subject died as a result of the AE (whether or not the AE is related to the device or procedure)

15.2.4 Expectedness (Anticipatedness)

An anticipated AE is an effect which by nature, occurrence, severity or outcome has been identified as a possible complication associated with the investigational medical device and/or intervention procedure.

Potential AEs that are reasonably anticipated to occur during the cardiac EP procedure are listed in table 6. These events should be reported via EDC as anticipated AEs. Anticipated AEs are to be reported to the sponsor via EDC as indicated in section 0.

Table 6: Comprehensive List of Anticipated Adverse Events

Anticipated Adverse Events	
(Acute) renal failure	Hypoxia
(Aspiration) pneumonia	Increased phosphokinase level
(Skin) laceration	Infection, localized
(Vascular) bleeding	Infection, systemic
Acute Respiratory Distress Syndrome (ARDS)	Ischemia
Air embolism	Local Hematoma/ecchymosis
Allergic reaction to contrast media	Localized skin reaction
Allergic skin reaction	Mitral Insufficiency
Altered Mental Status Confusion; Altered Level of Consciousness;	Myocardial infarction with or without ST elevation
Anemia	Nausea
Anesthesia complications/reactions	Palpitations
Anoxic or hypoxic encephalopathy	Papillary Muscle tear/injury
Aortic Puncture	Pericardial effusion resulting in tamponade
Apnea - sedation induced	Pericardial effusion without tamponade
Arrhythmia (new or worsening of pre-existing arrhythmia)	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 and/or injury	Pleural effusion
AV fistula	Pneumothorax
Back Pain	Post- and perioperative pain
Bronchial fistula, Broncho-pericardium fistula	Post Procedural Hematuria
Cardiac arrest	Pseudoaneurysm
Cardiac pacemaker insertion or replacement	Pulmonary edema
Cardiac perforation	Pulmonary embolism
Cardiac Tissue Injury	Pulmonary hypertension
Cardiac Valve Rupture/Damage	Pulmonary toxicity, like acute pulmonary syndrome
Cardiogenic Shock	Pulmonary vein dissection
Cerebro-Vascular accident (CVA)/Stroke	Pulmonary vein stenosis
Chest pain/discomfort	Renal Artery Stenosis
Complete or incomplete heart block	Respiratory arrest
Conduction block	Respiratory depression
Coronary Artery Stenosis	Respiratory failure
Coronary artery thrombosis	Respiratory infection
Death	Retinal Artery Embolism

Deep venous thrombosis	Retroperitoneal bleeding
Diaphragmatic paralysis	Sepsis
Dislodgement/Malfunction of pacemaker/defibrillator leads	Sinus bradycardia
Disseminated Intravascular Coagulation	Sinus tachycardia
Dizziness, presyncope, vertigo	Skin burn or necrosis
Dysphagia	Skin edema
Dyspnea	Skin or soft tissue (radiation) injury/tear
Endocarditis	ST segment changes
Epigastric Distress	Subclavian artery puncture
Epistaxis	Temperature elevation / Fever
Esophageal injury / perforation	Thrombocytopenia
Fatigue	Thromboembolism
Fluid overload	Thrombosis
Gastric hypomotility	Transient extremity numbness
Gastroesophageal reflux	Transient Ischemic attack (TIA)
Gastrointestinal disorders	Urinary Retention Postoperative
Gastrointestinal diverticulosis	Urinary tract injury or infection related to the urinary catheter
Gastroparesis	Valvular damage/insufficiency
Headache	Vascular (access) dissection (including coronary arteries)
Heart failure (acute or chronic)	Vascular Injury
Heart injury	Vascular occlusion
Heart valve insufficiency	Vascular Perforation
Hemoptysis	Vasovagal reactions
Hemorrhage	Ventricular Fibrillation
Hemothorax	Vessel damage/trauma
High/increased creatine phosphokinase (CPK)	Vessel perforation
Hypertension	Vessel spasm (including coronary arteries)
Hypervolemia	Visual disturbance
Hypotension	Worsening of pre-existing pulmonary disease
Hypovolemia	Wound healing disturbance

*Recurrence 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.

15.3 Time Period and Frequency for Event Assessment and Follow-up

The investigator, or designated individual, will record all reportable events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit.

All AEs, especially SAE's, need to be followed until the event is resolved (with or without sequelae), stabilization, or until the event is adequately explained. The medical monitor or designee of this clinical investigation will decide if more follow-up information is needed in case the event is not resolved at study completion. All required treatments and outcomes of the SAE must be recorded in the eCRF.

15.4 Reporting Procedures

15.4.1 Adverse Event Documentation and Reporting Requirements

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

Each AE must be reported to the sponsor regardless of classification, seriousness, intensity, outcome or causality. The investigator is responsible for ensuring that all AEs observed by the investigator, 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, Adverse Device Effects and Device Deficiencies section of this protocol (section 0). All AEs must be documented by completing subject's medical records (source documents) and appropriate eCRF by the investigator or study coordinator throughout the study and provided to the Sponsor. All AEs will be monitored until they are adequately resolved or explained.

Anonymized documentation pertaining to the AE (e.g. laboratory tests, consultation reports, post-mortem reports, new information relating to a previously reported AE, correspondence with the local EC, etc.) will be provided by the investigator to the sponsor or designee in a timely manner, when requested. Follow-up reports 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.

The Sponsor is responsible for the classification of AEs and ongoing safety evaluation of the study and shall review the investigator's assessment of all AEs. The sponsor will determine and document in writing their seriousness and relationship to the investigational device. In case of disagreement between the sponsor and the PIs, the sponsor shall communicate both opinions to the concerned parties.

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

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

Timing for reporting the different types of AEs is described in table 7.

Table 7: AE Reporting Requirements

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

Study device deficiency that could have led to a SAE *	Report to Sponsor immediately upon awareness of event but no later than 72 hours
All other Adverse Events	Report to Sponsor immediately upon awareness of event but no later than 2 weeks

* If a) suitable action had not been taken, or b) intervention had not been made or, c) if circumstances had been less fortunate.

15.4.2 Serious Adverse Events Reporting

All

- SADEs
- Investigational DD that might have led to a SAE if
    a) suitable action had not been taken or
    b) intervention had not been made or
    c) if circumstances had been less fortunate, whether or not they are related to the device or procedure,
- new findings/updates in relation to already reported events.

must be reported to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel.

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

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

The sponsor will report or ensure reporting all reportable events and updates to the reportable events to the EC (by the principal investigator) as per national or site-specific requirements. Event reporting to relevant CAs for non-CE-marked devices will occur by the sponsor and if indicated per local country requirements by the investigator.

15.4.3 Unanticipated Device Effect Reporting

All UADE/SADE/USADE **must be reported** to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel. An investigator shall submit to the reviewing EC a report of any UADE occurring during an investigation according to EC requirements.

15.4.4 Events of Special Interest

All study device deficiencies must be reported to the Sponsor, via eCRF, as soon as possible, within 72 hours by the study site personnel. If a device failure is detected or suspected, it should be documented on the eCRF and the device returned according to the Sponsor's instructions**.**

The investigational device should be sent to appropriate R&D team or designated Quality engineer. Complaints related to non-investigational products manufactured and/or distributed by Biosense Webster, used during the procedure related to other devices (other than the study device under investigation), are to be reported according to current Biosense Webster procedures and other policies as necessary (i.e., institutional policies, EC policies, and

local regulations). Investigators are instructed to return devices in accordance with current company procedures and other relevant regulations.

Event reporting to relevant CAs in accordance with the jurisdictional regulations will occur by the sponsor and/or by the investigator, depending upon the local requirements and will be done in EU per MDR 2017/745. Event reporting for European sites will be done through the Eudamed web form once fully functional. Until then, the template for the Clinical Investigation Summary Safety Report Form will be used (MDCG 2020-10/1). For Israeli sites, the event reporting will be sent to the applicable MOH inbox ct_compliance@MOH.GOV.IL or dsur@MOH.GOV.IL, as indicated per local country requirements.

A device deficiency related to a medical device not manufactured by Biosense Webster should be reported by the investigator to their respective manufacturer as per relevant regulation. Complaints related to non-Biosense Webster, Inc. products must be handled according to institutional policies, EC policies, and local regulations.

15.5 Safety Oversight

Safety oversight will be conducted as described in the Safety Management Plan. Aggregate safety data will be reviewed during enrollment by the study safety lead in order to promptly identify new issues or trends which may have an impact on the conduct of the study and/or subject safety. Under the rules as defined in the Safety Management Plan, safety events will be reviewed by the Safety Management Team which may recommend appropriate action(s) to ensure subject safety.

16. Administrative Responsibilities

16.1 Ethics Committee and Competent Authority Application

The study protocol (or amendment[s]), ICF, and other applicable study related documents must be approved by the EC and CAs before enrollment of subjects. Any additional requirement imposed by the EC or CA shall be discussed, agreed upon, and followed. A signed copy of the EC and CA approval letters addressed to the investigator must be submitted to Biosense Webster certifying study approval prior to subject enrollment. Biosense Webster and the EC must approve, in writing, any changes to the protocol that affect the rights safety and/or welfare of the subjects or may adversely affect the validity of the study.

In countries with a centralized submission process, a single submission will be performed in order to obtain the joint opinion from EC and CA. This applies for the initial application and for substantial modifications.

In addition, Biosense Webster, Inc. is responsible for notifying the relevant CA of the intention to perform a clinical investigation under this protocol and ensure to get the official response/ approval before starting the clinical investigation.

16.2 Audits and Inspections

The sponsor and/or designee and/or CAs may contact the participating institution to inform the investigator of an upcoming audit/inspection. The investigator should immediately notify the sponsor of any CA audits/inspection at the study site. The audit/inspection can include the review of documents, facilities, records and any other resources deemed by the authorities to be related to study.

17. Deviations from the Clinical Investigational Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures and evaluations described in this protocol. 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 EC requirements; failure to report AEs, product malfunctions and other product issues; and other non-conformance to GCP.

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. Waivers are prohibited for this clinical study. Protocol deviations will be monitored closely and will be reported per EC/CA requirement.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed without prior approval of the sponsor and EC. Such deviations shall be documented and reported to the sponsor and the EC as required.

All instructions described in this study protocol are to be followed. If an amendment is required, it must be made in written form and receive approval from all persons and authorities who approved the original protocol. Administrative changes (do not affect subject's benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original protocol recipients.

18. Investigational Product

18.1 Use of the Investigational Device and Investigator Experience

18.1.1 Training

The training of applicable clinical site personnel will be the responsibility of the Sponsor. 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 ablation.

To ensure uniform data collection and protocol compliance, the Sponsor will conduct a training session that will include reviewing the protocol, eCRF and data collection process, and the AE reporting process. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

18.1.2 Materials

Biosense Webster, Inc., is the legal manufacturer of the NUVISION™ NAV Ultrasound catheters to be used in this study. The investigational catheters are built in a clean room environment, and sterilized using EtO gas, in a manner similar to standard, commercially approved Biosense Webster products. Further detail of catheter components coming into contact with the human body are described in the Investigator Brochure.

Complete manufacturing records of every lot of catheters manufactured for human use during this study are maintained at the respective manufacturing location. Each lot of catheters is released for human use under a Confirmation of Conformity from Regulatory Affairs that will certify that the investigational catheters conform to the General Safety and Performance Requirements for product release apart from those features, that are being investigated in this clinical investigation. And that, with regards to these aspects, every precaution has been taken to protect the health and safety of the patient.

Nuvera Medical is the legal manufacturer of the NUVISION™ Connection Cables to be used in this study. The non-sterile investigational cables are built on a validated production line. Further detail of cable components and production process are described in the Investigator Brochure.

18.2 Device Acquisition and Accountability

After obtaining a fully executed clinical trial agreement and appropriate CA/EC approvals, the study site will receive the necessary amount of study-related materials prior to commencement. Study-related devices (investigational and non-investigational) will be shipped to the site upon completion of required documentation. Investigational Study Devices will be labeled as "**Investigational Device**" and are only to be used for subjects enrolled in this clinical study.

The Sponsor will keep records of all investigational devices shipped to the site. Investigational site personnel are responsible for appropriate logging of devices received, verification of packing slip information (i.e. lot numbers and quantity shipped) and date and identifying that each device was used in the study and disposition information completed when returned to the Sponsor.

The Investigational Device Accountability Log shall record the following information:

- Date of receipt
- Person in receipt of the devices
- Quantity received
- Catalog number
- Serial/lot numbers
- Expiry Date
- Date device was used
- Subject ID on whom device was used
- Date of return
- Reason for return (i.e. used without incident, malfunction, expired, end of study, …)

18.3 Device Returns

All investigational devices (**used and unused**) will be returned to the Sponsor's attention and per Sponsor's Instructions. Device deficiencies should be properly documented on the eCRF. Any suspected malfunctioning device or device associated with an AE (device related AE) will undergo a thorough complaint analysis. All returned devices must be properly labeled with the study name, the subject identification number, date of issue, identified as a defective return, non-defective return, or AE (as applicable). All tracking information must be retained in the event the package has been lost and requires tracking. All investigational devices should be returned.

19. 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 ICH-GCP, and with applicable regulatory requirement(s).

The sponsor will use a combination of remote contact and on-site monitoring. Each site will undergo periodic monitoring of the study, which involves a visit from a Sponsor representative, qualified to perform such visit. On-site monitoring visits will be performed as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun.

Monitoring visits may include, but are not limited to, the following:

- Protocol adherence
- Source documentation verification and accuracy of the eCRFs
- Safety events documentation and reporting
- Verification that informed consent is being obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the site file
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, etc.
- Compliance with applicable regulations
- Identification and action to resolve any issues or problems with the study.

The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. In addition to on-site monitoring visits, remote contacts can occur to follow-up on outstanding items. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Data are to be submitted promptly via e-CRF after collection. Missing or unclear data will be corrected as necessary throughout the trial. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or malfunctions are observed and reported.

20. Statistical Methodology

This section represents the Statistical Analysis Plan for this protocol. All analyses and subsequent details are described below.

20.1 Levels of Significance

All data will be summarized by descriptive analyses. No formal hypothesis testing will be performed. All confidence intervals will use the two-sided 95% confidence level unless otherwise stated.

20.2 Sample Size Justification

A sample size of 30 subjects will be enrolled to characterize the performance and safety of the Investigational catheter.

The sample size is selected based on previous experience with similar design in first in human assessments of multi-electrode mapping catheters. This study is meant to characterize the catheter's ability to perform safely in various types of arrhythmias. No clinical claims of effectiveness or patient outcomes will be made from this study.

[redacted]

20.3 Analysis Sets

Safety Analysis Set: The Safety Analysis Set will consist of all enrolled subjects who have undergone insertion of the NUVISION™ NAV Ultrasound catheter.

Per Protocol (PP) Analysis Set: The PP Analysis Set will include all enrolled subjects who met the study eligibility criteria and in whom assessments were performed with the NUVISION™ NAV Ultrasound catheter.

20.4 Analyses to be conducted

20.4.1 General Conventions

Standard descriptive summaries for continuous data include the number of observations with data, mean, standard deviation (SD), median, minimum, and maximum values. These will be referred to as "continuous summaries".

For categorical data, the count and percent will be provided. Percentages will be based on the number of subjects without missing data. For adverse event and device effects data, percentages will be based on the number of subjects in the analysis population being used in the analysis. This will be referred to as "categorical summaries".

20.4.2 Subgroups

Subjects may be further classified into the five subgroups if appropriate:

1. Scar-related Atrial Tachycardia
2. Persistent Atrial Fibrillation (PsAF)
3. Paroxysmal Atrial Fibrillation (PAF)
4. Ventricular Tachycardia (VT)
5. Premature Ventricular Complex (PVC)

20.4.3 Subject Disposition

Subject disposition will be summarized and listed for the subject categories defined in protocol section 10.3 for all subjects. Subject disposition will be summarized using categorical summaries. The number and percent of patients who are enrolled in the study, fail inclusion/exclusion criteria, are included in the safety, and per-protocol analysis sets, complete the study, and prematurely discontinue from the study will be presented. Patients who are prematurely discontinued will be summarized by primary reason for discontinuation.

20.4.4 Demographic and Baseline Characteristics

Demographic variables will include age and sex. Baseline characteristics will include the primary study arrhythmia/procedure and the number of previous ablation procedures. All demographic and baseline characteristics will be summarized using categorical and continuous summaries, as appropriate, for the Safety Analysis Set. A listing of subject demographic and baseline characteristics will be generated.

20.4.5 Medical History

Medical history will be presented using the Safety Analysis Set.

Cardiovascular (CV) and Thromboembolic/Cerebrovascular medical history will be collected and summarized using categorical summaries. Each subject will be counted once under each type of CV and/or thromboembolic/cerebrovascular medical history they have experienced.

The number of subjects with TTE performed and those with pericardial effusion will be presented using categorical summaries. The left ventricle ejection fraction and the maximum dimension of pericardial effusion will be presented in continuous summaries.

The number of subjects with an exam performed to assess the presence of thrombus and whether a thrombus is present will be summarized.

Other medical history, including NYHA class, occurrence of diabetes, and history of bleeding will be summarized similarly.

20.4.6 Analysis for Primary Endpoints

Primary Performance Endpoint is defined as the completion of imaging required for the study procedure with the NUVISION™ NAV Ultrasound Catheter without resort to non-study ultrasound device(s).

The number of subjects who successfully completed the procedure without resort to a non-study ultrasound device will be summarized overall and per procedure type (atrial ablation/ventricular ablation) for the PP Analysis Set.

A listing of the primary performance endpoint will be provided.

Primary Safety Endpoint is defined as the occurrence of serious adverse events related to the Investigational catheter within 7 days of index procedure. An SAE will be counted as related to the investigational catheter if the relationship to a study catheter is anything other than ‘Not Related’.

The number of subjects with SAEs related to the investigational catheter will be summarized in the Safety Analysis Set overall and per procedure type (atrial ablation/ventricular ablation) by System Organ Class and Preferred Term and level of relationship. All tables will present summaries both by subject and by event. If a subject has multiple occurrences of an event within a level of summarization, then for the by-subject summaries only a single occurrence will be counted at each level of summarization at the highest level of severity/relationship; for the by-event summary all events will be counted.

All investigational catheter related SAEs will be listed by System Organ Class and Preferred Term, severity, causality (defined as possible, probable or having a causal relationship to the device and/or procedure), anticipation and outcome.

20.4.7 Analyses of Secondary Endpoints

Secondary Safety Endpoints will be analyzed using the Safety Analysis Set:

- All Serious Adverse Events, excluding investigational catheter related SAE, during the 7-day follow-up period.
- All non-serious Adverse Events related to the investigational catheter during the 7-day follow-up period

The number of subjects experiencing serious adverse events excluding investigational catheter related SAE and the number of serious adverse events excluding investigational catheter related SAE will be summarized in the Safety Analysis Set overall and per procedure type (atrial ablation/ventricular ablation) using categorical summaries similar to the primary safety endpoint.

The number of subjects experiencing non-serious adverse events related to the investigational catheter and the number of non-serious adverse events related to the investigational catheter will be summarized in the Safety Analysis Set overall and per procedure type (atrial ablation/ventricular ablation) using categorical summaries similar to the primary safety endpoint.

All SAEs excluding investigational catheter related SAE and all non-serious AEs related to investigational catheter will be listed by System Organ Class and Preferred Term, severity, causality (defined as possible, probable or having a causal relationship to the device and/or procedure), anticipation and outcome.

A listing of device deficiencies including the category and timing of the device deficiency will also be provided. Each deficiency will indicate whether it results in an adverse event.

Physician feedback on deployment, maneuverability, navigational features and imaging quality acquired with the investigational catheter will be analyzed using the PP Analysis Set. A post-procedure survey will be administered. Each question/sub-question will be answered by the physician using a Likert scale of 1 to 7 (1=poor and 7=excellent) and will be summarized. The summary results of each question will be presented overall and per procedure type (atrial ablation/ventricular ablation) using continuous summaries. A by subject listing including all feedback results will be provided.

20.4.8 Additional Endpoints

Additional Procedural Data will be analyzed overall and per procedure type (atrial ablation/ventricular ablation) using the PP Analysis Set and include the following parameters:

- Whether Imaging for Left Atrium (LA) and Left Ventricle (LV) volume measurements was done;
- Total fluoroscopy time;
- Total duration of the procedure.

For each of the above procedural data, the denominator will be the number of subjects where assessments with the study device are performed.
Listings will be provided.

Additional safety data

All non-serious AEs not related to the investigational catheter will be listed by System Organ Class and Preferred Term, severity, causality (defined as possible, probable or having a causal relationship to the device and/or procedure), anticipation and outcome.

20.4.9 Handling of Missing Data

No missing data will be imputed in this study. All analyses will be performed using observed data.

21. Ethics and Protection of Human Subjects

21.1 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 (FDA), applicable European medical device regulation and the local government. For study under MDR, MDR2017/745 will be applicable, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
The Sponsor will also maintain compliance with GCP (ICH E6 (R2), 9 November 2016), the European standard EN ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Fortaleza 2013), Sponsor general duties (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]), maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b)]), and to local regulations where required.

- General Duties
  Biosense Webster's general duties consist of submitting the clinical investigation application to appropriate regulatory agencies, assuring that sites have received EC approvals prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained.

- Data Quality and Reporting
  Biosense Webster is responsible for providing quality data that satisfy federal regulations and informing proper authorities of serious unanticipated AEs and deviations from the protocol.

- Selection of Investigators
  All potential investigational sites will undergo an evaluation to ensure that the site has the appropriate facilities and personnel to conduct the study in compliance with the clinical investigational plan. Based on outcome of evaluation process, Biosense Webster will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

- Supplemental Applications
  As appropriate, Biosense Webster will submit changes in the Clinical Investigational Plan to the investigators to obtain all applicable re-approvals.

- Maintaining Records
  Biosense Webster will maintain copies of correspondence, data, adverse device effects and other records related to the study. Biosense Webster will maintain records related to the signed Investigator Agreements.

- Submitting Reports
  Biosense Webster will submit any required regulatory reports identified in this section of the regulation. This may include UADEs, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports and protocol deviations.

21.2 Informed Consent Process

21.2.1 Informed Consent Procedure and Documentation

Subjects informed consent must be obtained and documented according to the principles of informed consent in the latest version of the Declaration of Helsinki (Fortaleza, 2013), ISO 14155, and approved by the reviewing CA and EC.

Informed consent is mandatory and must be obtained from all subjects prior to their participation in the study.

Prior to screening or performing any study related procedures that are solely for the purpose of determining eligibility for this study, any potential benefits and risks of the study must be explained to the subject. Subjects will be informed about aspects of the study that are relevant to the subject's decision to participate. Subjects should be made aware that by signing the ICF, they are granting approval for study personnel to review their medical records and to collect/analyze personal medical information. Subjects should also be informed that study personnel will maintain confidentiality of the medical records at all times.

The ICF will be written in a native, non-technical, language that is understandable to the subject and is to be approved by the applicable EC prior to enrolling subjects. The subject or designee will be provided with ample time to read and understand the ICF and to consider participation in the study. Informed consent will be requested prior to enrollment and must be personally signed and dated by the subject, or subject's legal representative, prior to performance of any study related activity or procedure. If a subject is unable to read or write, informed consent shall be obtained through the aid of an independent witness who will be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective subject and, whenever possible, subject shall sign and date the ICF. The witness must also sign and date the ICF attesting that the information was accurately explained, and that informed consent was freely given. The point of enrollment corresponds with the time that the subject signs the informed consent.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and, where applicable, local and federal regulations. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial. Subjects or his/her legal representative must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the

satisfaction of the patient or the representative. Failure to provide written informed consent renders the subject ineligible for the study. If new information becomes available that can significantly affect a subject's future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing the amended ICF.

21.3 Participant and Data Confidentiality

During this clinical investigation, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Biosense Webster concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized Biosense Webster personnel or representatives (including contracted service providers, i.e. Core Lab, Clinical Research Associate, CRO, etc.), representatives of the FDA or CAs acting in their official capacities will have access to these confidential files upon request (including, but not limited to, laboratory test result reports, ECG reports, admissions/discharge summaries for hospital admission occurring during a patient's study participation and autopsy reports for deaths occurring during the clinical investigation). Some of the countries to which the study subjects and investigators personal data may be transferred may not offer as comprehensive a level of protection of personal data as within the European Union but Sponsor will take all reasonable steps to ensure a sufficient level of data protection. All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

21.3.1 Research Use of Stored Data

- Intended Use: Data collected under this protocol may be used to study AF.
- Storage: Access to stored data will be limited. Data will be stored using codes assigned by the sponsor. Data will be kept in password-protected computers. Only investigators and the sponsor will have access to the data.

22. Source Documents and Access to Source Data/Documents

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, other hospital or investigator office/clinic documents, and system data (CARTO and ultrasound system). If unique study parameters are not documented on standard hospital or office reports, a worksheet may be developed to record this information. The worksheet shall be signed by the PI or authorized designee and will serve as source document and as basis for monitoring the eCRFs. Electronic subject records will be considered as source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records should be printed and added to the subject's paper file. A print-out of a completed eCRF cannot be used as source documentation.

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.

Only authorized Biosense Webster personnel or representatives, authorized site personnel, local government authorities, or the FDA, acting in their official capacities, will have access to these confidential files.

23. Quality Assurance 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 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 CAs.

24. Data Handling and Record Keeping

24.1 Data Collection and Management Responsibility

The Sponsor will be responsible for all data management activities. These activities include development of an 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.

24.1.1 Data Collection

eCRFs will be used to collect all subject data during this clinical investigation. eCRFs have been developed to capture the information outlined in this clinical investigation Plan. Modification to the eCRF will only be made if deemed necessary by the sponsor. Data on these eCRFs will be monitored (source verified) and the monitor will ask the site representative to correct if necessary, to match the source documents. All 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 used to provide analysis of this clinical investigation.

24.1.2 Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are timely and properly recorded on each subject's eCRF and related documents. The investigator, or a designated individual, is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data. Completed eCRF 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 and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the governing EC and Biosense Webster.

Table 8: Responsibilities for Preparing and Submitting Reports

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

It is recommended that all eCRF data be entered by the designated site personnel as soon as possible. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines noted within this clinical investigation protocol.

24.1.3 Data Verification and Review

Biosense Webster 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 will be queried as necessary throughout the trial. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or device malfunctions/complaints are observed and reported. Biosense Webster will be responsible for auditing the database and confirming the overall integrity of the data.

24.1.4 Final 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.

24.2 Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 10 years or per country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed. This documentation must be accessible upon request by the CAs, 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 EC must be notified in writing of the name and address of the new custodian. Record retention dates must be provided to all parties by the sponsor's corporation.

25. Study Completion, Suspension or Termination

The study end shall be deemed to coincide with the last visit of the last subject. The sponsor will inform the responsible CA within 15 days of the study end in a participating country. In addition, each CA will be notified within 15 days of the global study end.

This study may be temporarily suspended or prematurely terminated at the discretion of the Sponsor. The Sponsor may also terminate a site prior to study completion if the Sponsor believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by EC). If the study is prematurely terminated or suspended, the PI will promptly inform the EC and will provide the reason(s) for the termination or suspension. The sponsor will inform within 15 days the responsible CA and provide a justification in accordance with MDR Article 77.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The PI and sponsor shall keep each other informed of any communication received from either the EC or the CA.

If early termination of the study is required due to safety concerns, each site will undergo a monitoring visit 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. Any enrolled subjects will continue to be followed per the study protocol requirements.

If, for any reason, the sponsor suspends or prematurely terminates the study at an individual study site, the sponsor shall inform the responsible CA as appropriate and ensure that the EC is notified, either by the PI or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other PIs. The sponsor will inform within 24 hours the responsible CA and provide a justification in accordance with MDR Article 77.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the sponsor, EC and regulatory agency.

A clinical study report will be submitted within one year of the study end or within three months of the suspension or premature termination.

26. Data and Publication Policy

Publications and/or presentation of clinical investigation results will be coordinated and governed between Biosense Webster, Inc., the clinical investigation author(s) and if applicable local law. 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.

As per ISO 141155: 2020 paragraph 5.4. a description of this clinical investigation will be registered in publicly accessible database (http://www.ClinicalTials.gov) and content shall be updated throughout the study. Results will be entered at completion of the clinical investigation.

27. Document Filing

A copy of all approved versions of the Investigation Protocol will be kept, by the site, in the Investigator Site File and in the Sponsor Trial Master File.

28. Scientific References

[1] G. Perk, R. M. Lang, M. A. Garcia-Fernandez, J. Lodato, L. Sugeng, J. Lopez, et al., "Use of real time three-dimensional transesophageal echocardiography in intracardiac catheter based interventions," *J Am Soc Echocardiogr,* vol. 22, no. 8, pp. 865-882, Aug 2009.

[2] F. F. Faletra, G. Pedrazzini, E. Pasotti, S. Muzzarelli, M. C. Dequarti, R. Murzilli, et al., "3D TEE during catheter-based interventions," *JACC Cardiovasc Imaging,* vol. 7, no. 3, pp. 292-308, Mar 2014.

[3] E. Anter, J. Silverstein, C. M. Tschabrunn, A. Shvilkin, C. I. Haffajee, P. J. Zimetbaum, et al., "Comparison of intracardiac echocardiography and transesophageal echocardiography for imaging of the right and left atrial appendages," *Heart Rhythm,* vol. 11, no. 11, pp. 1890-1897, Nov 2014.

[4] G. Rigatelli, F. Dell'Avvocata, M. Giordan, N. Viceconte, R. A. Osanna, G. Braggion, et al., "Usefulness of intracardiac echocardiography with a mechanical probe for catheter-based interventions: a 10-year prospective registry," *J Clin Ultrasound,* vol. 42, no. 9, pp. 534-543, Nov-Dec 2014.

[5] B. A. Medford, N. W. Taggart, A. K. Cabalka, F. Cetta, G. S. Reeder, D. J. Hagler, et al., "Intracardiac echocardiography during atrial septal defect and patent foramen ovale device closure in pediatric and adolescent patients," *J Am Soc Echocardiogr,* vol. 27, no. 9, pp. 984-990, Sep 2014.

[6] R. Kabra and J. Singh, "Recent trends in imaging for atrial fibrillation ablation," *Indian Pacing Electrophysiol J,* vol. 10, no. 5, pp. 215-227, May 2010.

[7] W. Lee, W. Griffin, D. Wildes, D. Buckley, T. Topka, T. Chodakauskas, et al., "A 10-Fr ultrasound catheter with integrated micromotor for 4-D intracardiac echocardiography," *IEEE Trans Ultrason Ferroelectr Freq Control,* vol. 58, no. 7, pp. 1478-1491, Jul 2011.

[8] F. E. Silvestry, M. B. Kadakia, J. Willhide and H. C. Herrmann, "Initial experience with a novel real-time three-dimensional intracardiac ultrasound system to guide percutaneous cardiac structural interventions: a phase 1 feasibility study of volume intracardiac echocardiography in the assessment of patients with struc," *J Am Soc Echocardiogr,* vol. 27, no. 9, pp. 978-983, Sep 2014.

[9] M. Alkhouli, Z. Chaker, A. Fahad, R. Saleem and R. Bryan, "Outcomes of Routine Intracardiac Echocardiography to Guide Left Atrial Appendage Occlusion," *JACC Clin Electrophysiol,* vol. 6, no. 4, pp. 393-400, Apr 2020.

[10] T. Flautt, A. Da-Wariboko, A. Lador, A. Patel, M. Guevara and M. Valderrábano, "Left Atrial Appendage Occlusion Without Fluoroscopy: Optimization by 4D Intracardiac Echocardiography," *JACC Cardiovasc Interv,* vol. 15, no. 15, pp. 1592-1594, Aug 2022.

[11] S. S. Kim, Z. M. Hijazi, R. M. Lang and B. P. Knight, "The use of intracardiac echocardiography and other intracardiac imaging tools to guide noncoronary cardiac interventions," *J Am Coll Cardiol,* vol. 53, no. 23, pp. 2117-2128, Jun 2009.

[12] T. Bartel, S. Muller, A. Biviano and R. T. Hahn, "Why is intracardiac echocardiography helpful? Benefits, costs, and how to learn," *Eur Heart J,* vol. 35, pp. 69-76, Jan 2014.

[13] C. Gianni, J. E. Sanchez, D. G. Della Rocca, A. Al-Ahmad, R. P. Horton, L. Di Biase, et al., "Intracardiac Echocardiography to Guide Catheter Ablation of Atrial Fibrillation," *Card Electrophysiol Clin,* vol. 13, no. 2, pp. 303-311, Jun 2021.

[14] D. Fornell, "First-in-Human Experience With Novel 4D ICE Catheter For Catheter Ablation and LAA Closure Procedures," 05 Aug 2021. [Online]. Available: https://www.dicardiology.com/content/first-human-experience-novel-4d-ice-catheter-catheter-ablation-and-laa-closure-procedures. [Accessed 18 Oct 2022].

[15] H. Calkins, G. Hindricks, R. Cappato, Y. H. Kim, E. B. Saad, L. Aguinaga, et al., "2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary," *J Arrhythm,* vol. 33, no. 5, pp. 369-409, Oct 2017.

[16] R. L. Bick and E. P. Frenkel, "Clinical aspects of heparin-induced thrombocytopenia and thrombosis and other side effects of heparin therapy," *Clin Appl Thromb Hemost,* vol. 5, no. 1, pp. s7-s15, Oct 1999.

[17] B. Cox, M. E. Durieux and M. A. Marcus, "Toxicity of local anaesthetics," *Best Pract Res Clin Anaesthesiol,* vol. 17, no. 1, pp. 111-136, Mar 2003.

[18] R. S. Gruchalla, "10. Drug allergy," *J Allergy Clin Immunol,* vol. 111, no. 2, pp. s548-s559, Feb 2003.

[19] P. M. Mertes and M. C. Laxenaire, "Allergic reactions occurring during anaesthesia," *Eur J Anaesthesiol,* vol. 19, no. 4, pp. 240-262, Apr 2002.

[20] S. K. Morcos, H. S. Thomsen and J. A. Webb, "Prevention of generalized reactions to contrast media: a consensus report and guidelines," *Eur Radiol,* vol. 11, no. 9, pp. 1720-1728, Jul 2001.

[21] A. C. Lin and D. J. Wilber, Complications Associated With Radiofrequency Catheter Ablation, in Radiofrequency catheter ablation of cardiac arrhythmias: basic concepts and clinical applications, S. H. a. D. Wilber, Ed., Armonk, N.Y.: Futura Publishing Co. Inc., 2000, pp. 737-746.

[22] M. M. Scheinman and S. Huang, "The 1998 NASPE prospective catheter ablation registry," *Pacing Clin Electrophysiol,* vol. 23, no. 6, pp. 1020-1028, Jun 2000.

[23] P. L. Mar, L. Chong, A. Perez, D. Lakkireddy and R. Gopinathannair, "Entrapment of diagnostic catheter within Advisor HD grid mapping catheter," *J Cardiovasc Electrophysiol,* vol. 32, no. 3, pp. 860-861, Mar 2021.

[24] R. Cappato, H. Calkins, S. A. Chen, W. Davies, Y. Lesaka, J. Kalman, et al., "Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation," *Circ Arrhythm Electrophysiol,* vol. 3, no. 1, pp. 32-38, Feb 2010.

[25] E. P. Gerstenfeld, P. Guerra, P. B. Sparks, K. Hattori and M. D. Lesh, "Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers," *J Cardiovasc Electrophysiol,* vol. 12, no. 8, pp. 900-908, Aug 2001.

[26] P. Kovoor, M. Ricciardello, L. Collins, J. B. Uther and D. L. Ross, "Risk to patients from radiation associated with radiofrequency ablation for supraventricular tachycardia," *Circulation,* vol. 98, no. 15, pp. 1534-1540, Oct 1998.

[27] G. T. Nahass, "Fluoroscopy and the skin: implications for radiofrequency catheter ablation," *Am J Cardiol,* vol. 76, no. 3, pp. 174-176, Jul 1995.

[28] H. Calkins, L. Niklason, J. Sousa, R. El-Atassi, J. Langberg and F. Morady, "Radiation exposure during radiofrequency catheter ablation of accessory atrioventricular connections," *Circulation,* vol. 84, no. 6, pp. 2376-2382, Dec 1991.