# COVER PAGE

for posting publicly Localize Protocol on ClinicalTrials.gov web site

**Protocol title:** ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)

**Protocol code:** PM007

**Protocol date and version:** October 5, 2017 – Ver AB

**NCT number:** 03232645

# ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)

## CLINICAL INVESTIGATION PLAN

## PM007

**Sponsored By**

Boston Scientific Corporation
4100 Hamline Ave. N.
St. Paul, MN 55112

and

Guidant Europe NV,
RM Clinical Department
Green Square
Lambroekstraat 5D
1831 Diegem,
Belgium

# Contact Information

| Role | Contact |
|---|---|
| **Clinical Contact** | **Clinical Trial Managers, Protocol Authors**<br>Giovanni Raciti<br>Sr. Clinical Trial Manager<br>Guidant Europe, a Boston Scientific Company<br>Green Square, Lambroekstraat 5D<br>1831 Diegem<br>Belgium<br>Tel. +39 34 82 50 26 87<br>Giovanni.raciti@bsci.com<br><br>Elke Sommerijns<br>Sr. Clinical Trial Manager<br>Guidant Europe, a Boston Scientific Company<br>Green Square, Lambroekstraat 5D<br>1831 Diegem<br>Belgium<br>Phone: +32 479 76 71 56<br>Elke.sommerijns@bsci.com |

**Original Release:** July 12, 2017

**Current Version:** October 5, 2017

## Revision History

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| **AA** | **July 12, 2017** | **90702637 Ver AH** | **/** | **/** | **Initial release** |
| **AB** | **October 5, 2017** | **90702637 Ver AH** | **Protocol Synopsis and Section 8.1**<br><br>**Section 20.1** | **/** | **The number of sites was increased from 5 to 6.**<br><br>**Cardiovascular/ Procedure Related SAEs were deleted as reportable events: since all Serious Adverse Events have to be reported in the study, Cardiovascular /Procedure Related SAEs are anyhow considered as reportable events.**<br><br>**Clarification was added regarding reporting requirements for additional ablation procedures.**<br><br>**Clarification was added regarding reporting requirements for new arrhythmias.** |

## 2. Protocol Synopsis

| **ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)** | |
|---|---|
| **Study Objective(s)** | The objective of the study is to collect data on the use of the Rhythmia™ HDx mapping system running commercially available Software Version 2.0 or any future commercially available Software Version with DirectSense™ technology and the IntellaMap Orion™ mapping catheter in patients indicated for ablation treatment for de-novo Paroxysmal Atrial Fibrillation (PAF). The study will collect specific information to characterize the DirectSense technology in subjects undergoing catheter-based endocardial mapping and ablation for de-novo PAF using a commercial Rhythmia HDx mapping system. The clinical local impedance data will be used in order to generate usage guidance on the DirectSense local impedance feature in the management of de-novo PAF cases requiring Pulmonary Vein Isolation (PVI) and in order to further develop a future lesion indexing feature. |
| **Planned Indication(s) for Use** | • The Rhythmia mapping system and IntellaMap Orion mapping catheter are indicated for catheter-based atrial and ventricular mapping. The mapping system allows real-time visualization of intracardiac catheters as well as display of cardiac maps in a number of different formats. The IntellaMap Orion high-resolution mapping catheter is indicated for electrophysiological mapping (recording or stimulating only) of the cardiac structures of the heart.<br>• The IntellaNav MiFi OI ablation catheter is indicated for electrophysiological cardiac ablation procedures.<br>Subjects undergoing standard of care catheter-based endocardial mapping and ablation for de-novo PAF using a commercial Rhythmia™ HDx mapping system will be selected for this study. |
| **Devices Used in the Study** | • Commercial Rhythmia HDx System ;<br>• Commercially available Software Version 2.0 with DirectSense technology or any commercially available updates that are released during the course of the study;<br>• The IntellaMap Orion mapping catheter;<br>• The IntellaNav MiFi OI ablation catheter<br>NOTE: the study will not start until all study devices are market |

| **ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)** | |
|---|---|
| | released and commercially available in the regions where the study is conducted. |
| **Study Design** | The LOCALIZE study is a prospective, non-randomized, multi-center study to assess the DirectSense technology for the Rhythmia HDx mapping system. |
| **Planned Number of Subjects** | Enrollment will be considered as complete when 60 patients underwent the index ablation procedure and had all 4 Pulmonary Veins encircled (TREATMENT subjects, protocol section 10.3). To reduce the impact of individual center bias, each site may perform up to 30 procedures. |
| **Planned Number of Investigational Sites / Countries** | Up to sites in EU. |
| **Primary Endpoint(s)** | Association between baseline Local Impedance/Local Impedance drop values per anatomical segment* as recorded at index ablation procedure and the proportion of gaps per anatomical segment* as measured at the month 3 assessment.<br>* Eight segments around each PV pair defined as per **Figure 11.5-2** |
| **Secondary Endpoint(s)** | Additional analyses are planned, including but not limited to:<br>• Correlate DirectSense parameters and acute PVI gaps<br>o Acute isolation gaps per anatomical segment as associated with baseline Local Impedance and Local Impedance drop values at first pass encircling during the index ablation procedure<br>• Median number of gaps per patient (or per PV pair) after initial encircling;<br>• Statistical characterization of impedance readings for each ablation point<br>• Anatomical distribution of the gaps and impedance reading differences at different anatomical sites (PV segments*)<br>** Eight segments around each PV pair defined as per **Figure 11.5-2*** |

**ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)**

**Method of Assigning Patients to Treatment**

Subjects indicated for ablation treatment of de-novo PAF will be selected based on the inclusion/exclusion criteria and if deemed to be eligible for participation, will be asked to sign the Informed Consent Form.

Subjects who meet the eligibility criteria and have signed and dated the Informed Consent Form are considered enrolled in the study.

For all enrolled subjects who undergo the ablation procedure, the subjects will be treated with the commercial Rhythmia HDx System with commercially available Software Version 2.0 with DirectSense technology (or any commercially available updates that are released during the course of the study); the IntellaMap Orion mapping catheter and the IntellaNav MiFi OI ablation catheter.

**Follow-up Schedule**

Each subject undergoing PVI will be followed at index procedure, at pre-discharge visit, at the month 3 assessment and at month 4 follow up. The visit at three months after index procedure will include an invasive evaluation with the Rhythmia Mapping system to evaluate residual conduction gaps after PVI. The study will be considered complete after all enrolled subjects have completed the month 4 follow up.

**Data Collection Overview**

| Data Collected | ENROLLMENT/ BASELINE | INDEX PROCEDURE (Day 0) | PRE-DISCHARGE (0-7 days post procedure) | MONTH 3 FOLLOW UP (90± 21 days) | MONTH 4 FOLLOW UP (120± 30 days) | ADDITIONAL PROCEDURE *(if applicable)* | ADDITIONAL VISIT *(if applicable)* |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Inclusion/Exclusion | X | | | | | | |
| Demographic data | X | | | | | | |
| Medical History | X | | | | | | |
| Medication Regimen | X | X* | X* | X* | | X* | |
| Mapping and procedure data | | X | | X | | X** | |
| Patient status | X | X | | X | X | X | |
| Protocol Deviations | X | X | X | X | X | X | X |
| Adverse Event/ Device Deficiency Reporting*** | X | X | X | X | X | X | X |

| **ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)** | |
|---|---|
| | **Medication changes only will be captured*<br>***If additional procedure includes an additional ablation procedure in the LA with Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter.*<br>**** For details on Adverse Event and Device Deficiency reporting, please refer to Section 20.* |
| **Study Duration** | Enrollment is expected to be completed in approximately 6 months; therefore the total study duration is estimated to be approximately 10 months. |
| **Key Inclusion Criteria** | • History of recurrent symptomatic PAF with ≥1 episode reported and documented within the 365 days prior to enrollment; PAF is defined as AF episodes that last ≥30 seconds in duration and terminate within 7 days.<br>• Refractory or intolerant to at least one Beta Blocker, Calcium Channel Blocker, Class I OR Class III anti-arrhythmic drug (AAD);<br>• Eligible for an ablation procedure with the Rhythmia HDx mapping system (software version 2.0 or any future commercially available Software Version), IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter according to current international and local guidelines (and future revisions) and per physician discretion;<br>• Subjects who are willing and capable of providing informed consent;<br>• Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center;<br>• Age 18 to 80 |
| **Key Exclusion Criteria** | • Diagnosed with any of the following heart conditions within 90 days (3 months) prior to enrollment:<br>a. New York Heart Association (NYHA) Class III or IV<br>b. Left ventricular ejection fraction (LVEF) <35%<br>c. Left atrial (LA) diameter >5.5 cm<br>d. Unstable angina or ongoing myocardial ischemia (OMI)<br>e. Transmural myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), or valve or coronary bypass grafting surgery<br>• Active systemic infection or sepsis; |

| **ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)** | |
|---|---|
| | • Undergone any left atrial heart ablation procedure, either surgical or catheter ablation<br>• Prosthetic or stenotic valves in the chamber where the intended mapping will occur, or in the path of the catheter access route<br>• Subject has a Left Atrial Appendage Closure (LAAC) or Percutaneous Transcatheter Closure of a Patent Foramen Ovale (PFO)<br>• Subject has persistent or long-standing persistent atrial fibrillation (AF) ( >1 AF episodes lasting greater than 7 days, with no episodes having lasted greater than 30 days, within the past year)<br>• Life expectancy ≤ 6 months per physician judgment<br>• Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the sponsor to determine eligibility;<br>• The subject is unable or not willing to complete follow-up visits and examination for the duration of the study;<br>• Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion). |
| **Statistical Methods** | |
| **Primary Statistical Hypothesis** | No formal pre-specified statistical hypotheses will be tested in this study. |
| **Statistical Test Method** | Descriptive statistics will be used for baseline, procedure and follow-up data collected throughout the study. For the primary endpoint, 95% confidence intervals for the difference of the means will be used to compare DirectSense parameters between segments with and without gaps at month 3. |
| **Sample Size Parameters** | A sample size of 60 subjects is chosen to generate 50 patients with usable data (20% attrition) and have 90% power to detect a minimum difference in DirectSense parameters of 3.71 ohms between segments with and without gaps at month 3. |

| **ELectrical COupling Information From The Rhythmia™ HDx Mapping System And DireCtSense™ Technology In The Treatment Of Paroxysmal AtriaL FibrIllation- A Non-RandomiZed, ProspEctive Study (LOCALIZE)** | |
|---|---|
| **Required Medication Therapy** | This study has no specific requirements in terms of medication therapy; the standard of care medication regimen at the investigational site is being followed. |
| **Risks and Benefits** | The anticipated Adverse Events (AE) and Adverse Device Effects (ADE) in the LOCALIZE study are the same shared for the procedures of ablation with use of a 3D mapping system. There may be no direct benefit to the subject. However, a dedicated workflow to assess ablation gaps at index procedure and at the month 3 assessment may ensure durable isolation of the Pulmonary Veins, with potential long term effects on efficacy of ablation. |

## 3. Table of Contents

### 3.1. *Table of Figures*



### 3.2. *Table of Tables*

# 4. Introduction

The incidence and prevalence of cardiac arrhythmias have seen significant growth in the last few decades, largely mirroring a sharp increase in the forms of heart disease known to promote rhythm abnormalities. Tachyarrhythmias are estimated to affect well over 6 million people in Europe and the US and create an annual multi-billion dollar burden on these economies[1-2-3]. Atrial fibrillation (AF) is the most common tachyarrhythmia. It currently affects approximately 2.3 million people in North America[4] and 4.5 million people in Europe[5-6-7].

Traditional treatment modalities, such as drug therapy and open heart surgery, have been found to be inadequate for a growing number of patients, either because of poor efficacy, side effects, or the mere invasiveness of surgery[8-9-10]. The introduction of specialized percutaneous catheters and the development of other enabling technologies have collectively led to an improvement in the safety and efficacy of minimally-invasive curative procedures, namely catheter ablation of cardiac arrhythmias, a procedure which involves a process of Electro-Anatomical Mapping and subsequent ablation of the culprit tissue area[11].

PVI is currently the most prevalent approach for catheter ablation of PAF. Long-term success of the procedure is diminished by arrhythmia recurrences occurring predominantly because of reconnections in previously isolated Pulmonary Veins (PVs)[12-13].

The Rhythmia HDx mapping system is designed for electroanatomical mapping in catheter ablation procedures by optimizing the need for speed and accuracy. The system is able to simultaneously acquire data from multiple electrodes. In addition, based on user-defined criteria, the system is able to efficiently acquire data over multiple cardiac beats. When used in conjunction with the Rhythmia mapping catheter, the system is able to acquire up to hundreds of points per minute leading to fast and detailed map creation.

Since its market release, physicians and users have gained experience with the Boston Scientific Rhythmia HDx mapping system in the human clinical setting. Boston Scientific has recently implemented the DirectSense feature within the Rhythmia HDx mapping system to provide a local impedance metric that aids the physician in assessing catheter localization relative to cardiac tissue.

Previous research[12-13-14-15-16] has shown a positive correlation between catheter contact force and durability of lesions in PVI for PAF. The DirectSense feature within the Rhythmia HDx mapping system provides a measure of the resistive load at the catheter-tissue interface and is highly sensitive to objects with dissimilar resistivity. This is different from the mechanical contact provided by contact force in that it also represents the potential for resistive heating during RF applications. DirectSense thereby provides electrical coupling information and is believed to better guide physicians during ablation procedures in order to create durable PVI lesions.

This study will evaluate the correlation between the local impedance information of the DirectSense feature during initial procedure and gaps at month 3 follow-up in a clinical environment.

The data of up to 60 subjects who will undergo ablation treatment for de-novo PAF will be evaluated; the operating physician will be blinded to the local impedance information of the

DirectSense feature during initial PVI encircling and then receive local impedance information during acute and follow-up gap closure for all cases.

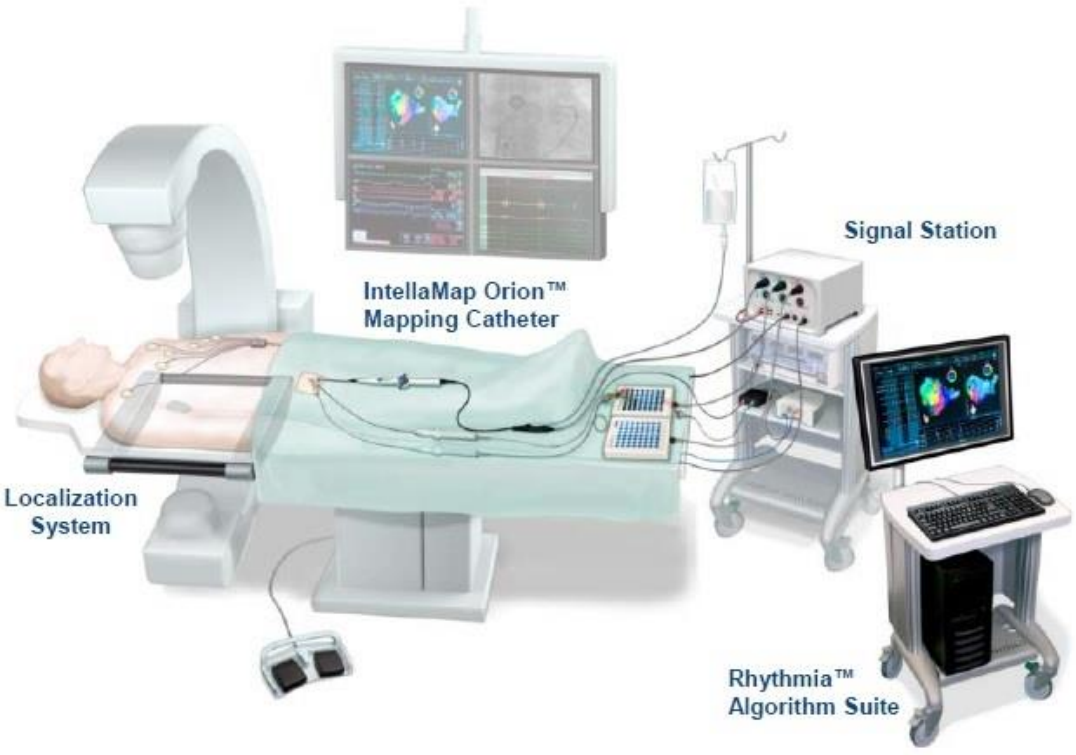
# 5. Device Description

All devices used in the study, including those described in section 5.1 to 5.3 are market released and commercially available in the regions where the study is conducted.

## 5.1. *Rhythmia HDx Mapping System*

The Rhythmia HDx mapping system and the IntellaMap Orion mapping catheter are designed for electroanatomical mapping in catheter ablation procedures. The Rhythmia HDx mapping System tracks catheters inside the heart in order to visualize their location and construct geometric shells. The Rhythmia HDx mapping system is also capable of using intra-cardiac location and electrical information to display electroanatomical maps - electrical activity information on the constructed geometry. Such electrical information can be visualized in 3D and in color. The Rhythmia HDx mapping system can display various types of electroanatomical maps including geometrical shell only, activation maps, voltage maps, and fractionation maps.

**Figure 5.1-1: The Rhythmia HDx Mapping System overview**



The System is able to simultaneously acquire data from multiple electrodes. In addition, based on user-defined criteria, the System is able to acquire data over multiple cardiac beats. When used in conjunction with the IntellaMap Orion Catheter, the System is able to acquire hundreds of points per minute leading to high resolution map creation.

The maps are constructed using catheter magnetic and impedance location technology and data from intracardiac electrograms. Maps may be displayed as anatomical maps, and electroanatomical maps.

The commercially available system operates the latest commercially-available software (version 2.0 or newer). Subsequent versions of the Rhythmia HDx mapping system and software may be used during this study as they become commercially available.

### 5.1.1. Key DirectSense Components.

The DirectSense feature allows for an impedance-based metric that can be used in conjunction with other clinical diagnostic measures (e.g., electrogram amplitude, fluoroscopy, intracardiac echocardiography, magnetic and impedance navigation, and tactile feedback) to inform catheter stability and navigation within the heart.

In the Rhythmia HDx mapping system, local impedance is measured using a traditional four-electrode method where a non-stimulatory current is driven between two electrodes (i.e., a source and a sink electrode) and the resulting potential field (voltage) is measured across two alternate electrodes on an intracardiac catheter. The driven current and the measured voltage are used to calculate impedance that represents local dielectric tissue properties nearest the source electrode. Using this method, far-field effects (e.g., respiration, patch placement, IV fluid infusion, etc.) have less influence on local impedance measurements than the more commonly used transthoracic impedance from radiofrequency (RF) generators. **Figure 5.1-2** demonstrates a representative four-electrode impedance measurement on the Boston Scientific MiFi catheter. In this example, the source electrode is configured to the tip of the catheter and the sink electrode is configured to the proximal ring (i.e., R3). Voltage is measured between the mini-electrodes embedded in the tip and the distal ring electrode (i.e., R1).

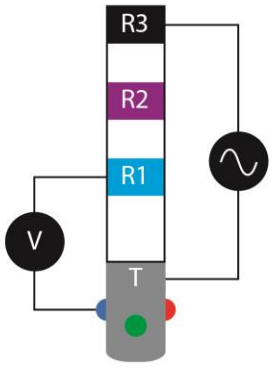



**Figure 5.1-2: Four-electrode impedance measurement on BSC MiFi Catheter**

This local impedance system utilizes existing Rhythmia HDx mapping system hardware capabilities and is completely independent of the RF generator impedance measurement system.
The graphical user interface (UI) for the Local Impedance feature is displayed in **Figure 5.1-3** during the creation of an anatomical map in the right atrium of a swine. This UI is comprised of four central elements:

(A) a local impedance vs time trace,

(B) an average impedance widget,

(C) a power bar, and

(D) a catheter tip graphic.

All display elements can be enabled or disabled per physician preference.

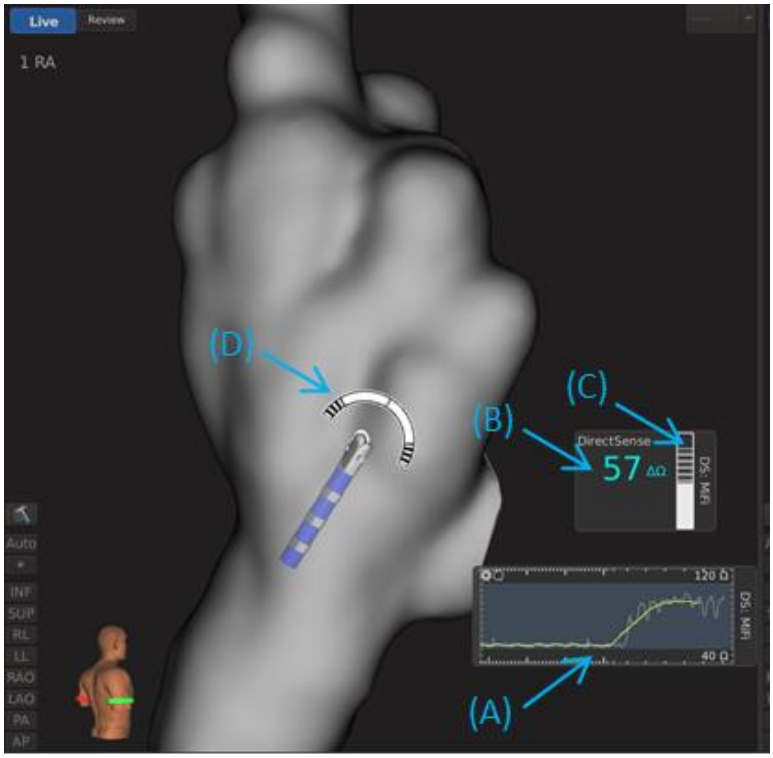



**Figure 5.1-3: Local Impedance feature user interface. A) Local impedance vs time trace. B) Average impedance widget. C) Power bar. D) Tip graphic.**

### 5.2. *The IntellaMap Orion High Resolution Mapping Catheter*

The IntellaMap Orion high resolution mapping catheter is indicated for electrophysiological mapping (recording or stimulating only) of the cardiac structures of the heart. The IntellaMap

Orion Catheter is an 8.5F (Ø 2.82 mm), 115 cm working length, 64-electrode steerable catheter. The basket-shaped distal region consists of 8 splines that comprise the electrode array. The catheter is supplied with an 8.5F insertion sleeve for insertion through the hemostasis valve of an introducer sheath. A sensor in the catheter tip enables the position of the distal region of the catheter to be tracked in space when used with the Rhythmia™ HDx mapping system.

### 5.3. *The IntellaNav MiFi OI Ablation Catheter*

The IntellaNav MiFi OI catheter is a steerable 7F catheter designed to deliver RF energy to the 4.5mm catheter tip electrode for cardiac ablation. It is designed to be used in conjunction with the Boston Scientific Irrigation Tubing Set (M0041160) or equivalent, Biosense Webster CoolFlow® Irrigation Pump with software version 1.3 or equivalent (Catalog CFP002 or CFP001/Model M-5491-00 or M-5491-01/02), Biosense Webster CoolFlow Irrigation Tubing Set (Model CFT001), Stockert EP-Shuttle RF Generator (Catalogue # 39D76X, software version 1.035, 1.036 and 10.037), Maestro 4000 Generator (Catalog M004 4000 0), MetriQ™ Irrigation Pump (Catalog M004 4100 0) and MetriQ™ Irrigation Tubing Set (Catalog M004117 0).

The IntellaNav MiFi OI catheter has a distal electrode segment and a proximal handle that are connected by a torquable catheter shaft. The electrode segment is comprised of a tip electrode and 3 ring electrodes. The tip electrode has an embedded temperature sensor and delivers RF energy for cardiac ablation. The tip electrode contains 3 embedded mini-electrodes that can record EGMs and deliver stimulus for pacing. The ring electrodes record electrograms (EGM) signals for mapping and deliver stimulus for pacing. The handle includes the electrical connector for the cable connection to the RF Generator, or 3-Dimensional (3D) mapping navigational system component, and one luer fitting used to connect the catheter to the irrigation system tubing set. The steering assembly, electrode lead wires, thermocouple wires and one cooling fluid lumen reside within the catheter shaft.

The IntellaNav MiFi OI catheter incorporates an open-irrigated cooling mechanism to remove heat from the catheter electrode tip and tip/tissue interface. Heparinized normal saline (0.9%) is delivered via one lumen in the catheter and infuses it into the heart through six ports on the distal portion of the catheter electrode tip.

# 6. Study Objectives

The objective of the study is to collect data on the use of the Rhythmia HDx mapping system running commercially available Software Version 2.0 or any future commercially available Software Version with DirectSense technology, the IntellaMap Orion mapping catheter and the IntellaNav MiFi OI ablation catheter, in patients indicated for ablation treatment for de-novo PAF. The study will collect specific information to characterize the DirectSense technology in subjects undergoing catheter-based endocardial mapping and ablation for de-novo PAF using a commercial Rhythmia HDx mapping system. Direct Sense data will be automatically recorded by the Rhythmia HDx mapping system during ablation procedures. The clinical local impedance data will be analyzed offline and used in order to generate usage guidance on the DirectSense local impedance feature in the management of de-novo PAF cases requiring PVI and in order to further develop a future lesion indexing feature.

# 7. Study Endpoints

## 7.1. *Primary Endpoint*

Primary endpoint is the association between baseline Local Impedance/Local Impedance drop values per anatomical segment as recorded at index ablation procedure and the proportion of gaps per anatomical segment as measured at the month 3 assessment.
Local impedance data will be automatically recorded by the Rhythmia HDx mapping system during PVI for each ablation point. Impedance data will be analyzed offline to determine *Baseline Local Impedance* and *Impedance drops* for each ablation point. For the primary endpoint assessment, impedance data will be grouped per 8 anatomical segments around each PV pair (please refer to **Figure 11.5-2**). Distribution of ablation points and gaps during the index ablation procedure and at the month 3 assessment will be recorded during mapping and ablation with the Rhythmia HDx mapping system.

## 7.2. *Secondary Endpoint*

Additional analyses are planned, including but not limited to:

- Correlate DirectSense parameters and acute PVI gaps;
    - Acute isolation gaps per anatomical segment as associated with baseline Local Impedance and Local Impedance drop values at first pass encircling during the index ablation procedure
- Median number of gaps per patient (or per PV pair) after initial encircling;
- Statistical characterization of impedance readings for each ablation point;
- Anatomical distribution of the gaps and impedance reading differences at different anatomical sites (PV segments)

# 8. Study Design

The LOCALIZE study is a prospective, non-randomized, multicenter study.

## 8.1. *Scale and Duration*

Enrollment will be considered as complete when 60 patients undergo the index ablation procedure and complete encircling of the 4 PVs (2 PV pairs). Up to 6 sites in EU may participate in the study. To reduce the impact of individual center bias, each site may perform up to 30 index ablation procedures. This limit of 30 procedures cannot be exceeded, unless Boston Scientific gives written approval to do so.

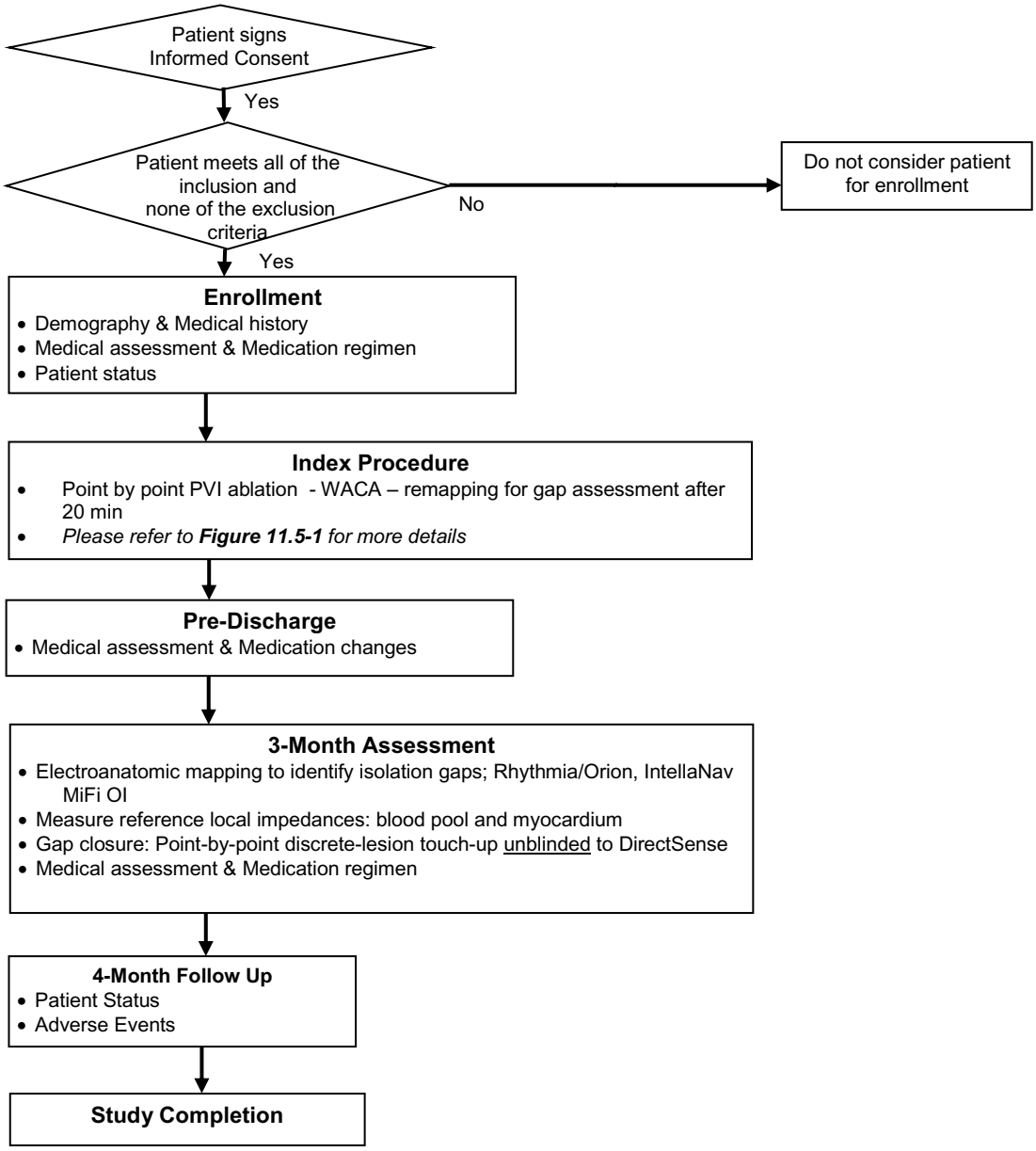
Each treated subject will be followed for 4 months after the index ablation procedure (index procedure); therefore treated subjects will be followed at index procedure, at pre-discharge visit, at the month 3 assessment and at month 4 follow up.

The study will be considered complete upon completion of the final month 4 follow-up.

A study subject's participation will be considered complete when all protocol required visits have been completed.

It is anticipated that enrollment will be conducted over a period of 6 months; therefore the total study duration is estimated to be 10 months.

**Figure 8.1-1: LOCALIZE Study Design**



### 8.2. *Treatment Assignment*

All subjects who meet the eligibility criteria as per 9.2 and 9.3 and sign the informed consent will be considered enrolled. Data will be collected during the baseline visit, the ablation (index) procedure, the pre-discharge visit, the month 3assessment and during the month 4 follow up. In case additional visits or additional ablation procedures take place, this data will also be collected. Please refer to Section 11.2 to 11.10 for an overview of data to be collected during these visits.

A study subject can only be enrolled once in the study.

#### 8.2.1. Treatment and Control

For all enrolled subjects who undergo the ablation procedure, the subjects will be treated with the commercial Rhythmia HDx System with commercially available Software Version 2.0 with DirectSense technology (or any commercially available updates that are released during the course of the study), the IntellaMap Orion mapping catheter and the IntellaNav MiFi OI ablation catheter. Initial encircling of the PVs will be performed by Investigators who perform the ablation blinded with respect to DirectSense (single blind masking). This will not impact the AE assessment by the investigator.

### 8.3. *Justification for the Study Design*

This is a post-market study designed to collect specific information in order to characterize the DirectSense technology in subjects undergoing catheter-based endocardial mapping and ablation for de-novo PAF using a commercial Rhythmia HDx mapping system. The DirectSense feature generates local impedance data that is automatically stored in the Rhythmia HDx mapping system during PVI. In this study local impedance data will be retrieved from the system for off-line analysis. As Direct Sense is intended to provide information on the localization of the ablation catheter to cardiac tissue (and the ability to create durable PV lesions), an additional endocardial mapping procedure at 3 month is required in this study in order to assess gaps in the PV, after substrate stabilization. This information will be used to evaluate the association between impedance readings at initial PVI and a durable isolation at 3 months (primary endpoint). This month 3 assessment is not standard of care in clinical practice, but a recognized standard for clinical studies and literature[18] in order to verify durable isolation of PV (acute assessment is unable to detect mid-term gaps). Subjects will be followed at month 4 for patient status/AE assessment.

# 9. Subject Selection

## 9.1. *Study Population and Eligibility*

Subjects enrolled in the LOCALIZE study will be clinically indicated for an endocardial catheter-based mapping procedure for the treatment of de-novo PAF and meet the study inclusion/exclusion criteria as outlined below in section 9.2 and 9.3. The subjects selected for participation will be from the investigator's general patient population. The investigator or its designee has the responsibility for screening all potential subjects and selecting those who meet study inclusion/exclusion.

## 9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 9.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

**Table 9.2-1: Inclusion Criteria**

| | |
|---|---|
| **Clinical Inclusion Criteria** | • History of recurrent symptomatic PAF with ≥1 episode reported and documented within the 365 days prior to enrollment; PAF is defined as AF episodes that last ≥30 seconds in duration and terminate within 7 days.<br>• Refractory or intolerant to at least one Beta Blocker, Calcium Channel Blocker, Class I OR Class III anti-arrhythmic drug (AAD);<br>• Eligible for an ablation procedure with the Rhythmia HDx mapping system (software version 2.0 or any future commercially available Software Version), IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter according to current international and local guidelines (and future revisions) and per physician discretion;<br>• Subjects who are willing and capable of providing informed consent;<br>• Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center;<br>• Age 18 to 80 |

## 9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 9.3-1**) will be excluded from this clinical study.

**Table 9.3-1: Exclusion Criteria**

| | |
|---|---|
| **Clinical Exclusion Criteria** | • Diagnosed with any of the following heart conditions within 90 days (3 months) prior to enrollment:<br>a. New York Heart Association (NYHA) Class III or IV<br>b. Left ventricular ejection fraction (LVEF) <35%<br>c. Left atrial (LA) diameter >5.5 cm<br>d. Unstable angina or ongoing myocardial ischemia (OMI)<br>e. Transmural myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), or valve or coronary bypass grafting surgery<br>• Active systemic infection or sepsis;<br>• Undergone any left atrial heart ablation procedure, either surgical or catheter ablation<br>• Prosthetic or stenotic valves in the chamber where the intended mapping will occur, or in the path of the catheter access route<br>• Subject has a Left Atrial Appendage Closure (LAAC) or Percutaneous Transcatheter Closure of a Patent Foramen Ovale (PFO)<br>• Subject has persistent or long-standing persistent atrial fibrillation (AF) ( >1 AF episodes lasting greater than 7 days, with no episodes having lasted greater than 30 days, within the past year)<br>• Life expectancy ≤ 6 months per physician judgment<br>• Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the sponsor to determine eligibility;<br>• The subject is unable or not willing to complete follow-up visits and examination for the duration of the study;<br>• Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion). |

# 10. Subject Accountability

## 10.1. *Point of Enrollment*

Subjects who meet the eligibility criteria and have signed and dated the Informed Consent Form are considered enrolled in the study. No further review of eligibility criteria for study participation is required beyond this point. It is the investigator's site responsibility to assess eligibility criteria before the index procedure.

## 10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to study device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Every effort should be made to retain subject enrollment for the duration of the study. During the informed consent process, subjects should be fully informed of the data collection requirements and duration, and should only be enrolled if willing to fully participate in it.

Reasons for withdrawal may include physician discretion, subject choice to retire consent, lost to follow-up, or death. In the event a subject does decide to withdraw from the study, every effort should be made to obtain full information on any on-going reportable Adverse Events up to the point of withdrawal. Subjects should only be considered lost to follow-up after significant effort has been made to contact the subject. For subjects who are "lost-to-follow-up" the investigator/center should have at least three documented attempts to contact the subject prior to completion of the "End of Study" eCRF. Subject withdrawal and lost to follow-up will be documented on the "End of Study" electronic Case Report Form (eCRF). Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason.

All open reportable Adverse Events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used, unless any local regulations apply which require removal of the data.

## 10.3. *Subject Status and Classification*

As subjects are evaluated, enrolled and treated in the study, they will be grouped into one of the following several categories. Categorization will help determine how data gathered from them will be stored and evaluated.

**Consent Ineligible**

A subject who has signed informed consent but does not meet eligibility criteria will be classified as "**Consent Ineligible**". There are no Follow Up reporting requirements for

consent ineligible subjects. Subjects determined to be Consent Ineligible according to statements above do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject Identification Number (ID) is created by Medidata Rave upon entering the subject in the eCRF. For consent ineligible subjects, an enrollment eCRF (ICF form and in-and exclusion criteria forms) and "end of study" eCRF form must be completed. If applicable, an Adverse Event eCRF form must be completed.

**Intent**
A subject who signs informed consent, meets eligibility criteria, but withdraws or is withdrawn prior to starting the encircling of the 4 PVs (prior to the 1st RF application in the left atrium) will be classified as "**INTENT**". Subjects that are enrolled in the study but do not undergo ablation procedure within 60 days from consent signature date are withdrawn from the study and classified as "**INTENT**".

There are no Follow Up requirements for Intent subjects. Intent subjects do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject ID is created by Medidata Rave upon entering the subject in the eCRF. For intent subjects, an enrollment, baseline and "end of study" eCRF form must be completed. If applicable, an Adverse Event eCRF form must be completed. No index procedure eCRF must be completed.

**Attempt**
A subject who signs informed consent, meets eligibility criteria and had the encircling of the 4 PVs started (post the 1st RF application in the left atrium), but did not have the initial encircling for all 4 PVs (2 PV pairs) completed will be classified as "**ATTEMPT**". Attempt subjects will be followed up until Pre-Discharge. A subject ID is created by Medidata Rave upon entering the subject in the eCRF. For Attempt subjects, all applicable case report forms must be completed. If applicable, an Adverse Event eCRF form must be completed. Attempt subjects do not count towards the enrollment ceiling and will not be used for analyses of the endpoints. The original signed Informed Consent must be maintained in the center's patient file.

**Treatment**
A subject who had encircling of the 4 PVs (2 PV pairs) completed will be classified as "**TREATMENT**". These subjects are followed in accordance with the follow-up schedule and included in all study analyses. A subject ID is created by Medidata Rave upon entering the subject in the eCRF. For Treatment subjects, all applicable case report forms per the protocol must be completed. Treatment subjects do count towards the enrollment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent and any relevant documentation must be maintained in the center's patient file.

It is the investigational sites's responsibility to list all Consent Ineligible, Intent, Attempt and Treatment subjects on the Screening and Enrollment Log.

# 11. Study Methods

## 11.1. *Data Collection*

Each Treatment subject will be followed at index procedure, at pre-discharge visit, at the month 3 assessment and at month 4 follow up. In order to reliably capture subject status at study end, the month 4 follow up has to be scheduled within 120 ± 30 days following the index procedure. If the subject needs to undergo an additional ablation procedure in the LA during the follow up period and the Rhythmia HDx mapping system, the IntellaMap Orion mapping catheter and the IntellaNav MiFi OI ablation catheter were used for this procedure, then this additional ablation procedure will be considered as the month 3 assessment if the month 3 assessment was not yet performed. No Protocol Deviation will have to be completed for a Visit Out Of Window. In case a different mapping system was used and/or different mapping and/or therapeutic catheters will be used for this additional ablation procedure in the LA, the subject will have to be withdrawn prior to this additional ablation procedure.

**Table 11.1-1** provides an overview of the data to be collected at each visit.

**Table 11.1-1: Data Collection Schedule**

| **Data Collected** | **ENROLLMENT/ BASELINE** | **INDEX PROCEDURE** (Day 0) | **PRE-DISCHARGE** (0-7 days post procedure) | **MONTH 3 FOLLOW UP** (90± 21 days) | **MONTH 4 FOLLOW UP** (120± 30 days) | **ADDITIONAL PROCEDURE** *(if applicable)* | **ADDITIONAL VISIT** *(if applicable)* |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Inclusion/Exclusion | X | | | | | | |
| Demographic data | X | | | | | | |
| Medical History | X | | | | | | |
| Medication Regimen | X | X* | X* | X* | | X* | |
| Mapping and procedure data | | X | | X | | X** | |
| Patient status | X | X | | X | X | X | |
| Protocol Deviations | X | X | X | X | X | X | X |
| Adverse Event/ Device Deficiency Reporting*** | X | X | X | X | X | X | X |

**Medication changes only will be captured*
***If additional procedure includes an additional ablation procedure in the LA with Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter.*
**** For details on Adverse Event and Device Deficiency reporting, please refer to Section 20.*

## 11.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation should be from the

investigator's general patient population. The investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

### 11.3. *Informed Consent/Enrollment Visit*

In order to determine eligibility of a subject, the investigator or designee needs to implement the consent process and verify/ document the subject meets the inclusion/exclusion criteria. Informed consent is required for all subjects (or their legal representatives) prior to their participation in the study. The subject should be given ample time to consider participation and ask questions if necessary. An approved informed consent form (ICF) shall be signed and personally dated by the subject (or legal representative). The original, signed document is to be kept with the subject's file and a copy must be provided to the subject. The index procedure must be performed within 60 days post ICF signature. In case the index procedure has not been performed within this time period, the subject will be classified as Intent (see section 10.3). The same subject cannot be considered for re-enrollment as re-enrollment is not allowed for any subjects in this study. The site will ensure that originally signed ICFs are filed in subjects' binders and that the ICF process is documented in the medical file. Originally signed ICFs and the ICF process will be made available for review at Interim Monitoring Visits (IMVs).

### 11.4. *Baseline Visit*

Subjects who provide consent and meet all of the study enrollment criteria will have baseline data collected.

The data collection at baseline includes:

- Visit date;
- Demographic data, including: age at time of consent, gender;
- Physical assessment including: height, weight, resting heart rate, systolic and diastolic blood pressure; medical history, including:
    - Underlying cardiovascular disease, including but not limited to hypertension, dyslipidaemia, cardiovascular artery disease;
    - Prior history of cardiac events including: acute myocardial infarction, ischemic stroke, hemorrhagic stroke or transient ischemic attack;
    - Prior surgical interventions and/or cardiac procedures (ablation excluded) including: Percutaneous Trans Catheter Angioplasty (PTCA), Coronary Artery Bypass Graft (CABG), pacemaker (PM) implantation, implantable cardioverter-defibrillator (ICD) implant, Cardiac Resynchronization Therapy (CRT) implant, cardiac valve interventions, left atrial appendage closure (LAAC), patent foramen ovale (PFO) intervention, heart transplant or procedures for implantation of other intracardiac devices;

- History of cardiac arrhythmias, including but not limited to time of first episode of PAF;
- Detailed history of all previous cardiac ablation procedures (catheter delivered or surgically performed), if any, including date of latest ablation procedure and any concomitant procedures (e.g., valve surgery, left atrial appendage closure or ligation, etc.), treated arrhythmia(s) and outcome;
- Pre-procedure assessment of Left Ventricular Ejection Fraction, and left atrial diameter, if available;
- Non-cardiac comorbidities

- CHA2DS2-VASc score
- Current cardiovascular medication regimen including anti arrhythmic, anticoagulation andantiplatelet agents.

### 11.5. *Index (ablation) procedure- Ablating physician BLINDED to DirectSense technology during initial encircling of PVIs (single blind masking)*

The index ablation procedure (day 0) should be performed using standard of care methods established by the investigational center (e.g. sterile technique, personnel requirements, etc.). Study-related mapping and ablation with the Rhythmia HDx mapping system, the IntellaMap Orion mapping catheter and the IntellaNav MiFi OI ablation catheter should only be performed by physicians trained in Electrophysiology (EP) and authorized by BSC to perform study-related activities.

#### 11.5.1. General information

The following general information on the procedure should be collected:

- Procedure date;
- Identification of study devices:
  - Commercial Rhythmia HDx System; serial number
  - Commercially available Software Version 2.0 with DirectSense technology or any commercially available updates that are released during the course of the study;
  - The IntellaMap Orion mapping catheter; catheter model, lot number
  - The IntellaNav MiFi OI ablation catheter; catheter model, lot number
- Identification of non-study devices:
  - Additional diagnostic catheters used during the case other than Orion including manufacturer, model and type
  - Sheaths used during the procedure including manufacturer, model and type

  - Additional ablation catheter(s) used during the case other than IntellaNav MiFi OI including manufacturer, model, and type
- If concomitant procedures occurred during ablation procedure (e.g. ICD implant, PM, LAAC);
- LA access approach (trans septal, retrograde)
- Was heparin administered prior to or immediately following LA access according to guidelines?[17]
- Were ACT levels of 300 to 400 seconds achieved during the procedure according to guidelines?[17]
- The name of the EP physician performing the procedure

### 11.5.2. Procedural information

In order to avoid potential bias, the number of ablating physicians performing the index procedure and the month 3 assessment per investigational site is restricted to 2. Boston Scientific will therefore authorize maximum 2 ablating physicians per site.

Prior to starting the ablations, Rhythmia HDx + IntellaMap Orion will be used to collect an electroanatomic map (i.e. activation and voltage map) of the Left Atrium.

For all subjects it is preferred that all maps are acquired during pacing from the Coronary Sinus.

11.5.2.1. PVI ablation(s) - *Ablating physician blinded to the DirectSense technology during initial encircling of PVs*

It is recommended to limit the space between the center of 2 lesions to a maximum of 5 mm. The ablating physician is encouraged to avoid jumps between anatomical locations.

For the PVI ablation(s) the following information will be collected:

- Information related to PVI ablation(s):
  - method of access to left atrium for ablation catheter, if applicable (trans-septal, retrograde, or both);
  - type of PVI ablation application(s) (e.g. point (focal) lesions, dragging lesions*);

    **The usage of dragging lesions for encircling the PVs will result in a Protocol Deviation. Dragging lesions or other types of applications are allowed for other arrhythmia(s)/ additional lines.*
  - specific PVI ablation technique(s) (WACA + information on additional lines if applicable)
  - anatomical segments targeted for ablation (please refer to **Figure 11.5-2** for the 8 circumferential positions around each PV pair)

    ***Not targeting all anatomical segments for ablation will result in a Protocol Deviation.*

- Total number of RF applications per anatomical segment for PVI ablation;
- Power and duration for each RF application (cfr. printed EP Lab Procedure Report);
- Occurrence of steam pops;
- DirectSense data collection:
    - Blood pool impedance measurements for approximately 10 s prior to the 1st RF application (reference measurement)
    - Myocardium impedance measurements for approximately 10 s prior to the 1st RF application (reference measurement)
    - Local impedance data will be sampled approximately every 50 ms. This data will be simultaneously recorded in a digital log file by the BSC representative.
    - Single ablation applications will be tagged by the Boston Scientific representative under guidance of the operating physician, in the Rhythmia HDx mapping system and on the Technical Source Form as:
        - belonging to a specific PV and anatomical segments.
        - resulting in steam pops.

      Single applications in each anatomical segment will be tagged with ordinal numbers.

At the end of the PVI ablation(s), PVI will be confirmed by means of entrance block.

The waiting period before testing entrance block should be approximately 20 minutes. After this waiting period, Rhythmia HDx + IntellaMap Orion will be used to collect an electroanatomic map (i.e. activation and voltage map) of the Left Atrium. For all subjects it is preferred that all maps are acquired during pacing from the Coronary Sinus.

The following information will be collected in the eCRF:

- Number and location of gaps for each PV per segment, if any***

*** *where feasible, the investigator should indicate approximate location respectively to the tagged ablation point*

The BSC Rhythmia Mapping Specialist (RMS) supporting the procedure will be unblinded to the DirectSense technology during the entire procedure.

If the ablating physician becomes unblinded to the DirectSense technology during the initial encircling of the PVs, this will have to be documented on the Technical Source Form. For more details on the Technical Source Form, please refer to Section 13.4.

*Gap closure, if applicable - Ablating physician UNBLINDED to the DirectSense technology*

If gaps are identified and the ablating physician decides to ablate these gaps, the ablating physician will be unblinded to the DirectSense technology.

It is recommended to limit the space between the center of 2 lesions to a maximum of 5 mm. The ablating physician is encouraged to avoid jumps between anatomical locations.

For the gap closure, the following information will be collected:

- additional point lesions

  **The usage of dragging lesions for encircling the PVs will result in a Protocol Deviation. Dragging lesions or other types of applications are allowed for other arrhythmia(s)/ additional lines.*

- anatomical segments targeted for gap closure (please refer to **Figure 11.5-2** for the 8 circumferential positions around each PV)

  ***Not targeting all anatomical segments for ablation will result in a Protocol Deviation.*

- Total number of RF applications per anatomical segment for gap closure;
- Power and duration for each RF application (cfr. Printed EP Lab Procedure Report);
- Occurrence of steam pops;
- DirectSense data collection:
  - Local impedance data will be sampled approximately every 50 ms. This data will be simultaneously recorded in a digital log file by the BSC representative.
  - Single ablation applications will be tagged by the Boston Scientific representative, under guidance of the operating physician, in the Rhythmia HDx mapping system and on the Technical Source Form as
    - belonging to a specific PV and anatomical segments
    - resulting in steam pops.

    Single applications in each anatomical segment will be tagged with ordinal numbers.
  - Local impedance data on the prior ablation line on both sides of the gap and on the gap itself must be recorded for approximately 10 s.

End of PVI

After touch ups of the gaps, Rhythmia HDx + IntellaMap Orion will be used to collect an electroanatomic map (i.e. activation and voltage map) of the Left Atrium. In case other arrhythmia(s)/additional lines will be ablated, these can be ablated prior to obtaining the electroanatomic map (i.e. activation and voltage map) of the Left Atrium. For all subjects it is preferred that all maps are acquired during pacing from the Coronary Sinus.

There is no requirement to implement a waiting period of approximately 20 minutes before obtaining this electroanatomic map. At the end of the PVI ablation(s), PVI will be confirmed by means of entrance block.

The following DirectSense data will be collected:

- Blood pool impedance measurements for approximately 10 s (reference measurement)
- Myocardium impedance measurements for approximately 10 s (reference measurement)
- Local impedance data will be sampled approximately every 50 ms. This data will be simultaneously recorded in a digital log file by the BSC representative.

The following information will be collected in the eCRF:

- Number of gap touch ups for each PV per each segment, if any****** *where feasible, the investigator should indicate approximate location respect to the tagged ablation point*

11.5.2.2. Ablation of other arrhythmia(s)/additional line(s)

In case other arrhythmia(s)/additional line(s) will be ablated, the PVI has to be achieved prior to ablating other arrhythmia(s)/additional line(s).

- If the other arrhythmia(s)/additional line(s) will be ablated in the LA, Rhythmia HDx + IntellaMap Orion will be used to collect an electroanatomic map (i.e. activation and voltage map) of the Left Atrium prior to ablating the other arrhythmia(s)/additional line(s) in the LA.

- If the other arrhythmia(s)/additional line(s) will not be ablated in the LA, the electroanatomic map (i.e. activation and voltage map) of the Left Atrium may be obtained after ablating the other arrhythmia(s)/additional line(s).

For the other arrhythmia(s)/additional line(s), the following information will be collected:

  - Type of ablation application(s) (e.g. point (focal) lesions, dragging lesions#);

    *#Dragging lesions or other types of applications are allowed for other arrhythmia(s)/additional lines.*
  - Anatomical locations targeted for other arrhythmia(s)/additional line(s);
  - Total number of RF applications per other arrhythmia(s)/additional location(s);
  - Technique used to ablate these other arrhythmia(s)/additional line(s);
  - Successful termination of the arrhythmia(s), if applicable;
  - Power and duration for each RF application;
  - Total RF application time for the other arrhythmia(s)/additional line(s);
  - Did steam pops occur;

11.5.2.3. Data collection after PVI ablation(s) and after ablation of other arrhythmia(s)/additional line(s), if applicable

At the end of the procedure the following information will be entered into the eCRF:

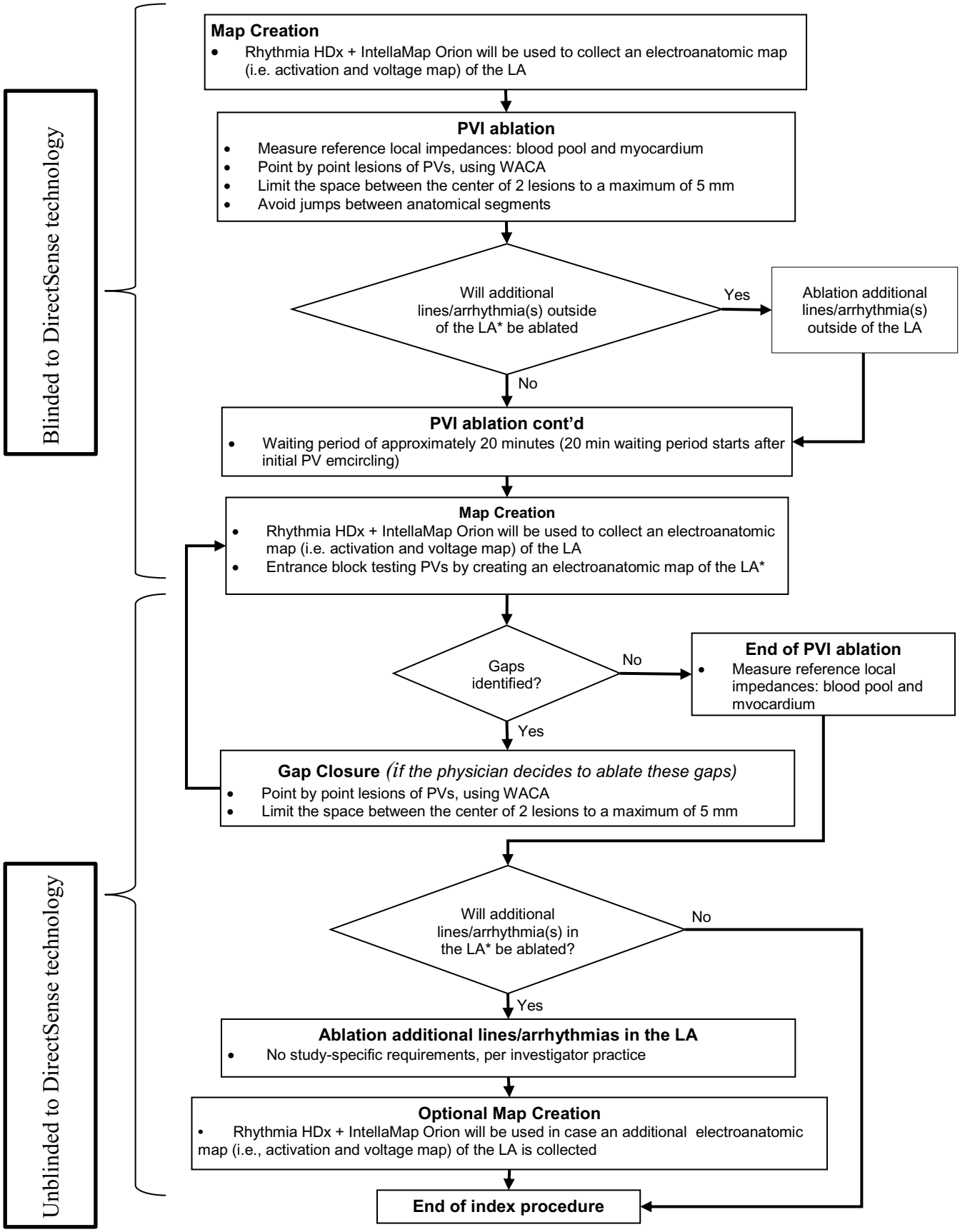
- Total Fluoroscopy time;
- Total procedure time will be collected, defined as time elapsed from time first access sheath insertion into the subject until the last catheter removed;
- Assessment of reportable Adverse Events/Device Deficiencies;
- Protocol Deviations, if applicable

At the end of the procedure, the following data must be saved/printed:

- The Rhythmia Advanced Export Case Data (the data collected through the Rhythmia HDx mapping system) will be saved and stored to external media, as provided by the sponsor.
- The EP Lab Procedure Report will be printed and stored in the center's patient file. Please refer to **Table 11.11-1** for an overview of source document requirements.

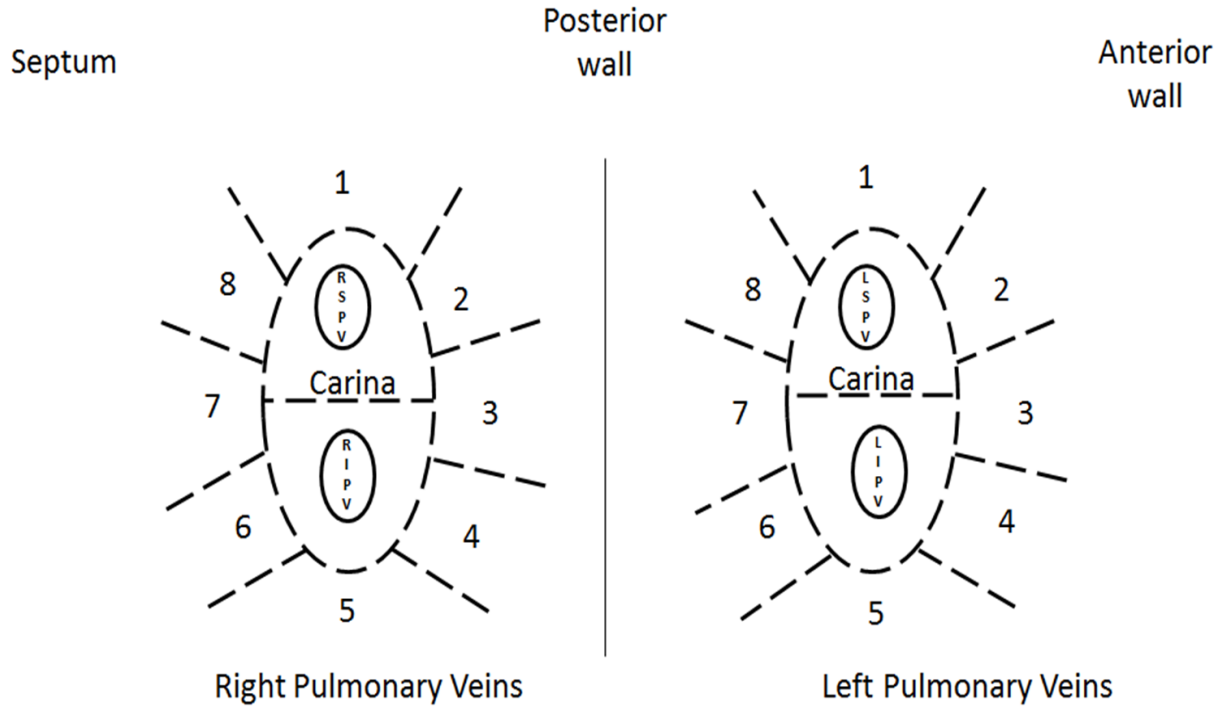
The Figure below describes the index procedure workflow.

**Figure 11.5-1: Index Procedure Workflow**




**If other arrhythmia(s)/additional line(s) will be ablated in the LA, Rhythmia + IntellaMap Orion will be used to collect an electroanatomic map of the LA prior to ablating the other arrhythmia(s)/additional line(s) in the LA. If the other arrhythmia(s)/additional line(s) will not be ablated in the LA, Rhythmia + IntellaMap Orion will be used to collect an electroanatomic map of the LA after ablating the other arrhythmia(s)/additional line(s).*

**Figure 11.5-2: 8 Circumferential positions around each PV**




### 11.6. *Pre-discharge visits*

The pre-discharge follow up visit should be done before hospital discharge but no later than 8 days past index ablation procedure, even if the subject has to remain at the hospital for a longer time (e.g. due to an Adverse Event).

The data collection at Pre-Discharge includes:

- Date of visit;
- Rhythm at time of pre-discharge;
- Variations in current medication regimen;
- Reportable Adverse Events, if applicable
- Additional Follow Ups/Procedures, if applicable

### 11.7. *Additional visits*

Additional visits before the month 4 follow up may occur per physician decision. If an additional visit should occur, the following information should be collected in the eCRF:

- Visit date;
- Type of visit: in-clinic or phone contact,
- Reportable Adverse Events, if applicable;
- Reason for additional follow up including standard of care, due to adverse event or other.

### 11.8. *Additional procedure*

In case an additional procedure occurs during the month 4 follow up period, the data of this procedure will be entered in the 'Additional Procedure' eCRF. In case this additional procedure is an ablation procedure (for the same, or different arrhythmias or for and unsuccessful ablation of the arrhythmia presented at index procedure) for which a different mapping system was used or different mapping and/or therapeutic catheters were used, detailed information about this additional ablation procedure will be entered in the 'Additional Procedure' eCRF:

- The name of the EP physician performing the procedure
- Was the additional ablation procedure performed in the LA?
    - For additional ablation procedures performed in the LA: Did this additional ablation procedure occur as a result of an unsuccessful or incomplete index procedure?
    - Was this additional ablation procedure performed to treat the same arrhythmia as the one from the index procedure? If no, specify the arrhythmia type
    - Was the Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter used for this additional ablation procedure?
        - If yes, this additional ablation procedure will be considered as the month 3 assessment if the month 3 assessment was not yet performed. This additional ablation procedure must be completed in the month 3 assessment visit. Please refer to Section 11.9-3 for more details.
        - If no, in case a different mapping system was used and/or different mapping and/or therapeutic catheters were used, the subject will have to be withdrawn prior to this additional ablation procedure.
        - Please refer to Section 10.2 for more details.

Any reportable adverse event resulting from additional procedures must be captured on the Adverse Event eCRF.

The additional ablation procedure itself should <u>not</u> be reported as a Serious Adverse Event (SAE), unless associated with subject worsening condition. In this case, the additional ablation procedure should be reported in the Adverse Event eCRF as corrective action of the specific SAE reported for the worsening condition.

Additional procedures will not alter the determination of the primary endpoint (acute procedural success), that will be based on the index procedure.

### 11.9. *Month 3 Assessment-Ablating physician UNBLINDED to DirectSense technology*

Rhythmia HDx + IntellaMap Orion will be used to collect an electroanatomic map (i.e. activation and voltage map) of the Left Atrium. In case gaps are detected and the physician decides to ablate these gaps, ablation must be performed with the IntellaNav MiFi OI catheter.

For all subjects it is preferred that all maps are acquired during pacing from the Coronary Sinus.

Gap sites will be determined for each segment and vein according to **Figure 11.5-2**. The location of each gap will be defined as a site of PV potential on the diagnostic catheter, and in the case of retreatment, to be confirmed by a change in PV activation.

The following DirectSense data has to be collected:

- Blood pool impedance measurements for approximately 10 s. In case the physician decides to ablate, this measurement has to be obtained prior to the 1st RF application (reference measurement)
- Non-ablated myocardium impedance measurements for approximately 10 s prior to the 1st RF application. In case the physician decides to ablate, this measurement has to be obtained prior to the 1st RF application (reference measurement)
- Local impedance data will be sampled approximately every 50 ms. This data will be simultaneously recorded in a digital log file by the BSC representative.

For at least 5 points that are considered as gap-free, the following DirectSense data has to be collected

- Ablated myocardium impedance measurements for approximately 10 s. In case the physician decides to ablate, this measurement has to be obtained prior to the 1st RF application (reference measurement)

For all gaps that are ablated, the following DirectSense data has to be collected:

- Gap impedance measurement for 10 s prior to first ablation within the gap

In case the ablating physician decides to ablate gaps, if any, the ablating physician can use whichever ablation technique he/she prefers. There is also no requirement to perform entrance block testing at the end of the ablation of gaps or to implement a waiting time after the ablation of gaps, if applicable. Also, there is no need to collect a Rhythmia + IntellaMap Orion activation map at the end of the ablation of gaps, if applicable.

### 11.10. *Month 4 Follow Up*

Investigators will have to assess subject status at one month (30 days +/-7) after the month 3 assessment. The month 4 follow up has to be performed in-clinic. The data collection at the month 4 follow up includes:

• Visit date;

• Current vital status of subject;

• Reportable Adverse Events, including resolution of ongoing events, if applicable

### 11.11. *Study Completion*

Each Treatment subject will be followed until the month 4 follow up. Participation in the study is considered complete upon completion of the month 4 follow up.
In case of premature termination of the study, please refer to Section 23.1.
Following termination/completion of the study, subjects will be managed according to local institution practice.

### 11.12. *Source Documents*

Printed, optical or electronic document containing source data shall be used; examples include hospital records, laboratory notes, radiographs, records kept at the investigation site, and/or at the laboratories involved in the clinical study, technical source forms (as defined in section 13.3)

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document. If the Principal Investigator delegates this task to one of the investigational team members, the delegation of this task must be documented in the Site Signature and Responsibility Log.

**Table 11.12-1: Source Documentation Requirements**

| Requirement | Disposition |
|---|---|
| Informed consent documentation process | Retain at Center |
| Documentation of:<br>• Demographics: age at procedure, gender<br>• Cardiovascular medications<br>• Arrhythmia history<br>• Cardiac disease history<br>• Pregnancy , if applicable | Retain at Center |
| Signed Technical Source Form for Index procedure and month 3 assessment | Retain at Center |

**Table 11.12-1: Source Documentation Requirements**

| Requirement | Disposition |
|---|---|
| Rhythmia Advanced Export Case Data | Submit to Boston Scientific |
| Printed EP Lab Procedure Report | Retain at Center |
| Procedure mapping data (saved to external media, as provided by the sponsor) | Retain at Center |
| In the event of patient death (if available):<br>• Death narrative<br>• Relevant medical records<br>• Death certificate<br>• Autopsy report | Submit one copy to Boston Scientific,<br>Retain one copy at center |

# 12. Statistical Considerations

An overview of the study design, sample size and statistical analysis is provided below.

## 12.1. *Endpoints*

### 12.1.1. Primary Endpoint

The primary endpoint is to assess the association between baseline Local Impedance/Local Impedance drop values per anatomical segment as recorded at index ablation procedure and the proportion of gaps per anatomical segment as measured at the month 3 assessment.

#### 12.1.1.1. Hypotheses

No formal pre-specified statistical hypotheses will be tested in this study.

#### 12.1.1.2. Sample Size

A sample size of 60 subjects is chosen to generate 50 patients with usable data (20% attrition) and have 90% power to detect a minimum difference in DirectSense parameters of 3.71 ohms between segments with and without gaps at month 3.

#### 12.1.1.3. Statistical Methods

While no formal hypothesis test will be performed, 95% confidence intervals for the mean difference in baseline Local Impedance/Local Impedance drop values between segments with and without gaps will used to compare groups.

## 12.2. *General Statistical Methods*

### 12.2.1. Analysis Sets

The primary endpoint will be assessed in all Treatment subjects who complete the month 3 gap site assessment.

Additional analyses will include all subjects enrolled into the study overall and categorized according to the definitions in section 10.3 or subsets of these categories.

#### 12.2.2. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient population. All patients meeting the eligibility criteria and having signed the ICF will be enrolled in the study.

#### 12.2.3. Number of Subjects per Investigative Site

To reduce the impact of individual center, each site may perform up to 30 index ablation procedures. This limit of 30 procedures cannot be exceeded, unless Boston Scientific gives written approval to do so.

### 12.3. *Data Analyses*

#### 12.3.1. Other Endpoints/Measurements

Additional analyses are planned, including but not limited to:

- Correlation of DirectSense parameters and acute PVI gaps
    - Acute isolation gaps per anatomical segment as associated with baseline Local Impedance and Local Impedance drop values at first pass encircling during the index ablation procedure
- Median number of gaps per patient (or per PV pair) after initial encircling;
- Statistical characterization of impedance readings for each ablation point
- Anatomical distribution of the gaps and impedance reading differences at different anatomical sites (PV segments)

#### 12.3.2. Changes to Planned Analyses

Any changes to the planned statistical analyses outlined in this protocol will be documented in the clinical study report along with a reason for the deviation.

## 13. Data Management

### 13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the Sponsor or its representative. The associated iMedidata RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies

pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

### 13.2. *Rhythmia HDx Electronic Data Management*

At the conclusion of the case, de-identified case data will be exported in a proprietary format from both the Rhythmia HDx mapping system to external storage media (as provided by the sponsor) and provided back to the sponsor.

### 13.3. *Data Retention*

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility, and BSC must receive written notification of this custodial change.

### 13.4. *Technical Source Forms*

A Technical Source Form (TSF) is developed by Boston Scientific or by the investigational site to capture protocol required data elements that are not duplicated in any other source documents. This form is to be used by the study sites as a source document. A Boston Scientific representative (R&D Representative or Clinical Trial Manager) may complete the TSF at the request of the Ablating Physician. The TSF will be reviewed and signed for approval by the Ablating Physician at the end of each procedure.

# 14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., EC/CA) of the revised protocol must be obtained prior to implementation.

# 15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor in the eCRF. Sites may also be required to report deviations to the EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including EC notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

# 16. Device/Equipment Accountability

The principal investigator or an authorized designee shall keep records documenting the

- Rhythmia HDx system unit number, software version used, date used
- Model number, serial number, and date used of the catheters

# 17. Compliance

## 17.1. *Statement of Compliance*

This study will be conducted in accordance with the current version of ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practice, relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

### 17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC requirements.

- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

#### 17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

### 17.3. *Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual EC approval and renewals will be obtained throughout the duration of the study as required by local/country or EC requirements. Copies of the Investigator's reports and the EC continuance of approval must be provided to the sponsor.

### 17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

#### 17.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during procedure, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including the Rhythmia HDx Mapping System, programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during ablation procedure, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following.

- Setting up, calibrating and/or operating parameters to investigator-requested settings of the Rhythmia HDx mapping system during the preparation and execution of the mapping and ablation procedure.
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel.

- Interaction with Boston Scientific noninvasive equipment (Rhythmia HDx System and, accessories) and interpretation of information contained therein to support the collection of required information by the delegated site staff.
- Print out reports directly from the System and provide original to clinical site as source documentation.
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.
- The R&D Representative or Clinical Trial Manager may complete the Technical Source Form during the procedure, in order to assist the ablating physician with data collection during the procedure.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to clinical protocol compliance.
- Reviewing collected data and study documentation for completeness and accuracy.

**Boston Scientific personnel will not do the following:**

- Practice medicine.
- Provide medical diagnosis or treatment to subjects.
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator.
- Collect critical study data (defined as primary or secondary endpoint data) without review and approval of the ablating physician.
- Enter data in electronic data capture systems or study medical data into paper forms.

### 17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

# 18. Monitoring

Monitoring (on-site and remote) will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits and audits and that sufficient time is devoted to the process.

# 19. Potential Risks and Benefits

## 19.1. *Anticipated Adverse Events and Adverse Device Effects*

The anticipated Adverse Events (AE) and Adverse Device Effects (ADE) in the LOCALIZE study are the same shared for the procedures of ablation with use of a 3D mapping system. Both the index ablation procedure and the three month invasive reassessment (a procedure of mapping and potential additional ablation) are associated with the same list of anticipated AE and ADE. Please refer to the study devices Directions for Use (DFU) for a listing of anticipated adverse events and adverse device effects associated with cardiac catheterization.

## 19.2. *Risks Associated with the Study Device(s)*

There are no incremental risks that are associated with the study devices and those of market available products as listed above.

## 19.3. *Risks associated with Participation in the Clinical Study*

Risks associated with participation to this study are similar to those shared with the standard ablation procedures. The impacts of study-specific differences in procedures are summarized as follows:

- The index ablation procedure performed in LOCALIZE has the same purpose of an ablation procedure of a subject not participating in this study (i.e. 3D mapping and ablation of PAF). The technique for ablation of the arrhythmia (WACA) is standard and can be further customized with additional ablation lines per physician's preference. The only differences with respect to a non-study ablation for PAF are:
    - Potential additional time required to collect information and impedance values for the DirectSense feature. The collection of impedance data will not affect therapy and will not add specific risks. The total prolongation of the procedure will not be

substantial and will not impact patient safety. In any case, the physician can decide to interrupt the procedure if any risk for the subject is expected due to the potentially prolonged procedure duration.

- The ablating physician will initially be blinded to the DirectSense feature when performing the initial encircling of the PVs. However, DirectSense data will be available to the ablating physician after re-mapping for potential additional gap closure. Having the feature blinded during initial encircling will not have an impact on patient's safety as the DirectSense feature is labelled as a localisation feature and not supposed to drive/guide the ablation therapy.

- The assessment at month 3 will be similar to the initial procedure as requiring mapping and potential ablation of the residual gaps. The ablating physician will not be blinded to DirectSense during this procedure. The additional procedure at month 3 will not present additional risks compared to a standard ablation procedure. An additional mapping and ablation procedure is currently not indicated for patients who underwent de novo ablation for PAF in the absence of symptoms or recurrence of arrhythmia. However, an additional ablation procedure after 2-3 months post initial PVI is currently a recognized standard used in previous studies[12,13] and has been included recent literature in order to verify durable isolation of PVs[18-22].

### 19.4. *Risk Minimization Actions*

Additional unanticipated risks may exist. Risks can be minimized through compliance with standard of care treatments, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

### 19.5. *Anticipated Benefits*

There may be no direct benefit to the subject. However, a dedicated workflow to assess ablation gaps at index procedure and at three months invasive reassessment may ensure durable isolation of the pulmonary veins, with potential long term effects on efficacy of ablation. The potential benefit for an additional mapping procedure at three months lies in the fact that the success rate after a single procedure is still sub-optimal as PV reconnection is frequently seen during repeat ablation[18-22]. As such, achieving durable chronic PV insulation by delivering effective, transmural lesions during the ablation is key to optimize long-term outcomes. Recently, the PRESSURE study[23] also showed that a strategy of routine repeated assessment with re-isolation of PV reconnection improved freedom from AT recurrence, AT burden, and quality of life compared with current standard care. Additionally, currently enrolled subjects may benefit from their participation in this study due to a closer follow up. Medical science and future patients may benefit from the results of this clinical protocol.

### 19.6. *Risk to Benefit Rationale*

Risk management activities, including hazard analyses, have been performed on Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter to identify and analyze known and foreseeable hazards and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and instructions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The hazard analysis has been reviewed and approved and the remaining risks are acceptable when weighed against the intended benefits to the patient.

## 20. Safety Reporting

### 20.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

**Reportable Events:**

- All Serious Adverse Events;
- All Events Leading to Death
- All Thromboembolic Events
- All Procedure Related AEs
- All Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter Device Related Adverse Events;
- All Device Deficiencies related to the study devices (Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter);
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the physicians manuals.

Whenever possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see **Table 20.2-1** for AE definitions).

If an additional ablation procedure is required, this additional ablation procedure should not be considered as an Adverse Event, unless associated with subject worsening condition or a new diagnosis. If the investigator considers this event to be related to any procedure, the event needs to be reported. In this case, the additional ablation procedure should be reported

in the Adverse Event eCRF as corrective action of the specific Procedure Related Adverse Event reported for the worsening condition or new diagnosis.

If the patient experiences a new arrhythmia between the index procedure and the end of study, and the investigator considers this Adverse Event to be procedure related, it needs to be reported.Refer to DFUs for the known risks associated with the study device(s).

The Boston Scientific Medical Safety group will provide safety oversight by reviewing and classifying individual events that are reported to the sponsor. Routine aggregate safety reviews will be conducted to ensure subject safety.

### 20.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 20.2-1**. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes. All events required to be reported in this study are listed in Section 20.1.

**Table 20.2-1: Safety Definitions**

| Term | Definition |
|---|---|
| Adverse Event (AE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/3* | Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.<br>NOTE 1: This includes events related to the investigational medical device or comparator.<br>NOTE 2: This definition includes events related to the procedures involved.<br>NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device. |
| Adverse Device Effect (ADE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/3* | Adverse event related to the use of an investigational medical device<br>NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.<br>NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device. |
| Serious Adverse Event (SAE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/3* | Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3.<br>Adverse event that:<br>a) Led to death,<br>b) Led to serious deterioration in the health of the subject <u>as defined by</u> either:<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, or<br>3) in-patient hospitalization or prolongation of existing hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body |

**Table 20.2-1: Safety Definitions**

| Term | Definition |
|---|---|
| | function<br>c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.<br>**NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event. |
| Serious Adverse Device Effect (SADE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/3* | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| Unanticipated Adverse Device Effect (UADE)<br><br>*Ref: 21 CFR Part 812* | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |
| Unanticipated Serious Adverse Device Effect (USADE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/3* | Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.<br>**NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. |
| Device Deficiency<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/3* | A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. |

Abbreviations: EC=Ethics Committee

### 20.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in **Table 20.3-1**:

**Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event**

| Classification | Description |
|---|---|
| **Not Related** | Relationship to the device or procedures can be excluded when:<br>- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;<br>- the event has no temporal relationship with the use of the investigational device or the procedures;<br>- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;<br>- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;<br>- the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);<br>- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error;<br>- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. |
| **Unlikely Related** | The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly Related** | The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably Related** | The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained. |
| **Causal Relationship** | The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:<br>- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;<br>- the event has a temporal relationship with investigational device use/application or procedures;<br>- the event involves a body-site or organ that<br>o the investigational device or procedures are applied to;<br>o the investigational device or procedures have an effect on;<br>- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);<br>- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);<br>- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; |

**Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event**

| Classification | Description |
|---|---|
| | - harm to the subject is due to error in use;<br>- the event depends on a false result given by the investigational device used for diagnosis, when applicable;<br>- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. |

### 20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 20.4-1**

Adverse events and device deficiencies must always be reported through the eCRF system. However, in the event that an alternative method of reporting is necessary (i.e. the eCRF system is unavailable), please report the adverse event or device deficiency to Boston Scientific by sending the Event Notification Form via email to the following email address:

**Localize.safety@bsci.com**

**Table 20.4-1: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline post-market studies* (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM) |
|---|---|---|
| Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect | Complete AE eCRF page with all available new and updated information. | • Within 1 business day of first becoming aware of the event.<br>• Terminating at the end of the study |
| Serious Adverse Event | Complete AE eCRF page with all available new and updated information. | • Within 10 business days after becoming aware of the event or as per local/regional regulations.<br>• For deaths, within 3 calendar days of site notification<br>• Reporting required through the end of the study |
| | Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor | • When documentation is available |
| Serious Adverse Device Effects | Complete AE eCRF page with all available new and updated information. | • Within 2 business days of first becoming aware of the event or as per local/regional regulations.<br>• Reporting required through the end of the study |
| | Provide all relevant | • When documentation is available |

| **Event Classification** | **Communication Method** | **Communication Timeline post-market studies*** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM) |
|---|---|---|
| | source documentation (unidentified) for reported event upon request of the sponsor. | |
| Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event. | Complete Device Deficiency eCRF with all available new and updated information. | • Within 2 business days of first becoming aware of the event. Reporting required through the end of the study |
| Adverse Event including Adverse Device Effects | Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device. | • In a timely manner (recommended within 30 business days after becoming aware of the information)<br>• Reporting required through the end of the study |

### 20.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) associated with the study devices (Rhythmia HDx mapping system, IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the study catheters will be provided in the Site Initiation Visit slides. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, a reportable event that results from a

device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

For Device Deficiencies, the investigator must assess and report if the device deficiency might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

### 20.6. *Reporting to Regulatory Authorities / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

### 20.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within3 calendar days of site notification. The site's EC must be notified of any deaths in accordance with that site's EC policies and procedures.

If requested by Boston Scientific, a detailed narrative (death letter) describing the circumstances surrounding the death should be included in the death notification. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

• Date and time of death;

• Place death occurred;

• Immediate cause of death;

• Rhythm at the time of death, if known (include any available documentation);

• Whether the death was related to the Rhythmia HDx mapping system, the IntellaMap Orion mapping catheter, IntellaNav MiFi OI ablation catheter clinical investigation, procedure, or subject condition;

• Whether or not the death was witnessed;

• Whether the subject had worsening heart failure; if applicable

• Any other circumstances surrounding the death;

• Approximate time interval from the initiating event to death (temporal course) – items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.

• Investigator or co-Investigator signature and date.

Also submit the following documentation, upon request from sponsor:

If the subject expired in the hospital:

• A copy of the medical records for that admission (e.g., H&P, consults, test results, operative reports, and/or progress notes from the hospital chart);

• Death certificate (if available);

• Autopsy report (if applicable);

If the subject expired outside of the hospital (e.g., home):

• A copy of the most recent clinic visit (if not already submitted to Boston Scientific);

• Death certificate (if available);

If applicable, the IntellaMap Orion mapping catheter and IntellaNav MiFi OI ablation catheter should be returned promptly to Boston Scientific RM/EP for analysis.

## 21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central EC, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,

- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC. The EC will determine the subject population to be re-consented.

The site will ensure that originally signed ICFs are filed in subjects' binders and that the ICF process is documented in the medical file. Originally signed ICFs and the ICF process will be made available for review at Independent Monitoring Visits (IMVs).

# 22. Suspension or Termination

## *23.1 Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

### 23.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

## *23.2 Termination of Study Participation by the Investigator or Withdrawal of EC Approval*

Any investigator, or EC in the LOCALIZE study may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

## *23.3 Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

### *23.4 Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed according to standard of care at the site. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

## 23. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

## 24. Reimbursement and Compensation for Subjects

### 24.1. *Compensation for Subject's Health Injury*

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, and if required by applicable law.

## 25. Bibliography

1. Huang SK, Wood MA, editors. Catheter ablation of cardiac arrhythmias. Philadelphia: Sounders Elsevier; 2006.

2. Kannel WB, Benjamin EJ. Status of Epidemiology of Atrial Fibrillation. Med Clin N Am 92 (2008) 17–40

3. Rhythmia Medical's analysis based on data from: Millennium Research Group.

4. Feinberg WM BJ, Laupacis A, et al. Prevalence, age distribution and gender in patients with atrial fibrillation; analysis and implications. Arch Intern Med. 1995;155:469-473

5. Wann S CA, January C, et al. ACC/AHA/HRS focused update on the management of patients with atrial fibrillation (2011 writing group members) (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2011;123:104-123

6. Fuster V RL, Cannom DS, et al. ACCF/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: Executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the North American Society of Pacing and Electrophysiology. Circulation. 2006;114:e257-e354

7. Friberg J BP, Scharling H. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14 666-672

8. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, Thorpe K, Champagne J, Talajic M, Coutu B, Gronefeld GC, Hohnloser SH. Comparison of beta-blockers, amiodarone plus beta- blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. 2006;295:165–71.

9. Waldo AL. A perspective on antiarrhythmic drug therapy to treat atrial fibrillation: there remains an unmet need. Am Heart J. 2006;151(4):771-8.

10. Noheria A, Kumar A, Wylie JV, Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation. Arch Intern Med. 2008;168(6):581-6.

11. Chen SA, Chiang CE, Tai CT, Cheng CC, Chiou CW, Lee SH, Ueng KC, Wen ZC, Chang MS. Complications of diagnostic electrophysiologic studies and radiofrequency catheter ablation in patients with tachyarrhythmias: an eight-year survey of 3,966 consecutive procedures in a tertiary referral center. Am J Cardiol. 1996;77(1):41-6.

12. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, Lambert H, Yulzari A, Wissner E, Kuck KH. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. Circ Arrhythm Electrophysiol. 2013 Apr;6(2):327-33. doi: 10.1161/CIRCEP.113.000374. Epub 2013 Mar 20.

13. Kautzner J, Neuzil P, Lambert H, Peichl P, Petru J, Cihak R, Skoda J, Wichterle D4, Wissner E, Yulzari A, Kuck KH. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. Europace. 2015 Aug;17(8):1229-35. doi: 10.1093/europace/euv057. Epub 2015 Jun 3.

14. Gaspar T, Sih H, Hindricks G, Eitel C, Sommer P, Kircher S, Rolf S, Arya A, Teplitsky L, Piorkowski C. Use of electrical coupling information in AF catheter ablation: a prospective randomized pilot study. Heart Rhythm. 2013 Feb;10(2):176-81. doi: 10.1016/j.hrthm.2012.10.010. Epub 2012 Oct 9.

15. Jones MA, Webster D, Wong KC, Hayes C, Qureshi N, Rajappan K, Bashir Y, Betts TR. The benefit of tissue contact monitoring with an electrical coupling index during ablation of typical atrial flutter--a prospective randomised control trial. J Interv Card Electrophysiol. 2014 Dec;41(3):237-44. doi: 10.1007/s10840-014-9943-6. Epub 2014 Sep 19.

16. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, Kantipudi C, Mansour MC, Melby DP, Packer DL, Nakagawa H, Zhang B, Stagg RB, Boo LM, Marchlinski FE. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. J Am Coll Cardiol. 2014 Aug 19;64(7):647-56. doi: 10.1016/j.jacc.2014.04.072.

17. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, et al. Europace. 2012 Apr; 14(4):528-606. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design.

18. Rordorf R, Expert Rev Med Devices. 2017; Liang, Expert Rev Cardiovasc Ther. 2016 , Aryana . Heart Rhythm. 2016 , Duytschaever Europace 2015, Reddy . J Cardiovasc Electrophysiol. 2015

19. Liang JJ, Santangeli P. Contact force sensing during atrial fibrillation ablation: clinical experience and effects on outcomes. Expert Rev Cardiovasc Ther. 2016 Jun;14(6):749-59.

20. Aryana A, Mugnai G, Singh SM, Pujara DK, de Asmundis C, Singh SK, Bowers MR, Brugada P, d'Avila A, O'Neill PG, Chierchia GB. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm. 2016 Feb;13(2):424-32.

21. Duytschaever M, Taghji P, Tavernier R. Towards durable pulmonary vein isolation: we are closing the gap. Europace. 2015 Aug;17(8):1164-5.

22. Reddy VY, Sediva L, Petru J, Skoda J, Chovanec M, Chitovova Z, Di Stefano P, Rubin E, Dukkipati S, Neuzil P. Durability of Pulmonary Vein Isolation with Cryoballoon Ablation: Results from the Sustained PV Isolation with Arctic Front Advance (SUPIR) Study. J Cardiovasc Electrophysiol. 2015 May;26(5):493-500.

23. Das M , Wynn GJ, Saeed Y, Gomes S, Morgan M, Ronayne C, Bonnett LJ, Waktare EP et al Pulmonary Vein Re-Isolation as a Routine Strategy Regardless of Symptoms The PRESSURE Randomized Controlled Trial. JACC 2017, In press.

# 26. Abbreviations and Definitions

## 26.1. *Abbreviations*

Abbreviations are shown in **Table 26.1-1.**

**Table 26.1-1: Abbreviations**

| Abbreviation/Acronym | Term |
|---|---|
| ACT | Activated Clotting Time |
| AE | Adverse Event |
| AF | atrial Fibrillation |
| AFL | atrial Flutter |
| ADE | Adverse Device Effect |
| AV | Atrio-Ventricular |
| BSC | Boston Scientific Corporation |
| CA | Competent Authority |
| CABG | Coronary Artery Bypass Graft |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CRT | Cardiac Resynchronization Therapy |
| CTI | Computerized Tomography Imaging |
| CTM | Clinical Trial Manager |
| DFU | Directions For Use |
| ID | Identification Number |
| EC | Ethics Committee |
| EDC | Electronic Data Capture |
| ECG | Electrocardiogram |
| EGM | Electrogram |
| EP | Elektrophysiology |
| GCP | Good Clinical Practice |
| HCP | Health Care Personnel |
| IC | Intracardiac |
| ICD | Implantable Cardioverter Defibrillator |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| IMV | Independent Monitoring Visit |
| IRB | Institutional Review Board |
| LAAC | Left Atrial Appendage Closure |
| MRI | Magnetic Resonance Imaging |
| PAF | Paroxysmal Atrial Fibrillation |
| PFO | Patent Foramen Ovale |
| PM | Pacemaker |
| PTCA | Percutaneous Trans Catheter Angioplasty |
| PV | Pulmonary Vein |
| PVI | Pulmonary Vein Isolation |
| RF | Radiofrequency |
| SAE | Serious Adverse Event |

**Table 26.1-1: Abbreviations**

| Abbreviation/Acronym | Term |
|---|---|
| SADE | Serious Adverse Device Effect |
| SR | Sinus Rhythm |
| SVT | Supraventricular Tachycardia |
| VT | Ventricular Tachycardia |
| UADE | Unanticipated Adverse Device Effect |
| USADE | Unanticipated Serious Adverse Device Effect |

### 26.2. *Definitions*

Terms are defined in **Table 26.2-2**.

**Table 26.2-2: Definitions**

| Term | Definition |
|---|---|
| Source Data | All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies). |
| Source Documents | Original documents, data, and records |

Abbreviations are defined in **Table 27.1-1**.

## 27. Appendices

Clinical trial organization, including names and addresses of the CRO(s) involved in selected geographies, names and addresses of the sites, names of Principal Investigators and clinical research monitors are provided as annex to the present protocol, and available upon request, where needed, to fulfill local requirements.