LUX-Dx™ Insertable Cardiac Monitor
Remote Programming and Performance Study

LUX-Dx PERFORM

C2045
CLINICAL INVESTIGATION PLAN

NCT #: 04732728

Sponsored By

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Vendors/Labs/External Organizations	A list of vendors/laboratories/External Organizations involved in the trial is maintained by the sponsor.

Original Release: June 4, 2020

Current Version: November 3, 2020

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	**June 4, 2020**	**92120219, Rev C**	**N/A**	**N/A**	Initial release for WIRB review and approval
B	**November 3, 2020**	**92120219, Rev D**	**2. Protocol Synopsis**	**Synopsis is updated to reflect changes made in the protocol main text.**	N/A
			4.2 Study Rationale	**Adding safety rationale and description of trial population.**	Adding clarification.
			5. LUX-Dx ICM Device/System Description	**Adding future device and system use.**	Adding clarification.
			6. Study Objectives and Endpoints	**Description of the safety endpoints and performance goals.**	Addition of the safety endpoints and performance goals.
			7.1. Scale and Duration	**Enrollment number, number of sites, definition of "Safety Cohort" and "Holter Cohort", and the resulting trial flowchart changes are described.**	Changes reflecting the new trial design.
			7.3. Justification for the Study Design	**Provide update and justification of the new enrollment number requirement.**	Study design update.
			8.2. Inclusion Criteria	**Clarify the 1st inclusion criteria and the new indication subgroup; list Holter study criteria separately for Holter subjects.**	Clarification; modification of indication subgroups.
			8.3. Exclusion Criteria	**List Holter study criteria separately for Holter subjects.**	Clarification.
			9.2. Enrollment Control	**Update enrollment control to 3 levels: Safety Cohort control, Holter Cohort control, and site control.**	Updates due to design changes.
			9.3. Withdrawal	**Adding 2 new withdrawal criteria to account for additional circumstances which subjects are considered withdrawn.**	Addition of withdrawal criteria.
			9.5. Subject Status and Classification	**Eligibility violation is considered a study deviation; safety check window is from 30 to 60 days after the attempted implant.**	Clarifications.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			10.1. Data Collection	**Visit activities and consolidated in the Data Collection Schedule table; virtual health visit option is added.**	Modifications and providing subject with additional visit option (virtual health visit).
			10.4. Enrollment Visit	**Clarify "Reason for Monitoring" determination.**	Clarifications.
			10.5. ICM Implant Procedure	**Adding implanter authorization requirement, R-wave amplitude collection, and evidence of device registration.**	Addition of requirement and clarifications.
			10.6. ICM Reprogramming	**Remove remote reprogramming required for the first 25-30 subjects, add cap of only requiring the first 5 reprogramming data entries, and clarify the requirement of finalization of the reprogrammed settings.**	Modifications of requirement and clarifications.
			10.7. 2-Month Holter Study Visit	**Provide option to conduct "Virtual Health Visit" in Holter study. Clarify two 6-day Holter are required for each Holter subject. Discuss the sample size requirement for the Holter study.**	Providing subject with additional visit option (virtual health visit); clarifications of Holter requirement and sample size needs.
			10.8. 6-Month and 12-Month EMR Review	**Provide option to conduct "Virtual Health Visit". Clarify lost to follow-up consideration due to lack of Clarity data transmission.**	Providing subject with additional visit option (virtual health visit); clarifications.
			10.9. LUX-Dx ICM Not in Service, Disabled, or Explanted	**Safety check window is from 30 to 60 days after the applicable events.**	Clarifications of requirement.
			11.1.1. Primary Effectiveness Objective 1 **11.1.2. Primary Effectiveness Objective 2**	**Sample size and statistical methodology for effectiveness objectives are updated to reflect the new trial design.**	Update due to new trial design.
			11.1.3. Primary Safety Endpoint – Acute	**Adding 2 new sections discussing the newly added safety endpoints for the study.**	Addition of safety endpoints for the study.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			11.1.4. Primary Safety Endpoint - Chronic		
			11.3.1. Interim Analyses	**Provide option for sample size re-estimation.**	Addition of study option.
			13.1. Data Collection, Processing, and Review	**Provide additional information on database lock.**	Additional information.
			13.3. Technical Source Forms (TSF)	**New section is added to provide additional information on TSF.**	Additional information.
			16.1. Statement of Compliance	**Provide additional information on clinical study agreement.**	Additional information.
			16.2. Investigator Responsibilities	**Provide additional information on investigator responsibilities.**	Additional information.
			16.4.1. Role of Boston Scientific Representatives	**Clarify the role of Boston Scientific Representatives.**	Clarifications.
			18. Potential Risks and Benefits	**Adding "Refer to the currently available LUX-Dx ICM User's Manual for an updated list of potential adverse events", and adding "Subject who participates in the Holter study may receive additional arrhythmia monitoring in the 14-day monitoring period by wearing the Holter monitor" as a potential benefit.**	Update the reference to the currently available User's Manual mid-study and addition of potential benefit.
			19.1. Reportable Events by Study Site to Boston Scientific	**Adding "Serious Adverse Device Effects" as reportable safety event for the study.**	Addition of reportable event.
			19.2. Definitions and Classification **19.3. Relationship to Device(s)**	**Definitions and Classification of adverse events and event relationship are updated per new ISO requirement.**	Update per new ISO requirement.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			19.4. Investigator Reporting Requirements	**Adding reporting requirement for "Serious Health Threat" and updating reporting timeframe for "Serious Adverse Event", "Serious Adverse Device Effects", "Device Deficiencies", and "Adverse Event".**	Updated study-specific requirement.
			21.1. Safety Monitoring Process	**Clarify the safety monitoring process.**	Clarifications.
			21.3. Independent Medical Reviewers – Arrhythmia Episodes **21.4. Independent Medical Reviewers – Safety Endpoints**	**Adding independent medical reviewers for arrhythmia episodes review and safety endpoints review.**	Adding independent medical reviewers.
			22.1.1. Criteria for Premature Termination of the Study	**Adding additional criteria for study termination.**	Addition of study criteria.
			23. Study Registration and Results	**Adding clinical study registration and clinical study report requirement.**	Addition of study requirement.
			24. Bibliography **25. Abbreviations and Definitions** **26. 1. Preliminary Data Collection Items**	**Tables and references are updated from Section 24 to 26.**	Updated information.
C	**November 4, 2020**	**92120219, Rev C**	**Version number**	**Updating document version number to correct a version error.**	Administrative update.

2. Protocol Synopsis

LUX-Dx Insertable Cardiac Monitor Remote Programming and Performance Study (LUX-Dx PERFORM)	
Study Objective(s)	The LUX-Dx PERFORM Study will characterize, in a general patient population, the utilization of the remote programming feature of the Boston Scientific (BSC) Insertable Cardiac Monitor (ICM) device. The study will also collect data to characterize the performance of arrhythmia detection algorithms. Finally, data collected will be used to analyze and characterize the ICM system-related safety events.
Indication(s) for Use	The LUX-Dx Insertable Cardiac Monitor (ICM) is intended to monitor and record subcutaneous electrocardiogram (S-ECG). The recorded S-ECG is used for the clinical evaluation and diagnosis of cardiac arrhythmias. The LUX-Dx is indicated for use in patients that have a known heart condition and are at risk of developing an abnormal heart rhythm, or have symptoms that may suggest a cardiac arrhythmia such as dizziness, palpitations, syncope, chest pain, and/or shortness of breath. The LUX-Dx ICM has not been tested specifically for pediatric use. LATITUDE Clarity™ is intended to remotely program and interrogate a compatible Boston Scientific device via the myLUX™ patient application (patient app) or LUX-Dx Clinic Assistant application (clinic app) and transfer data to a central database. The LATITUDE Clarity Data Management System provides patient data that can be used as part of the clinical evaluation of the patient.
Test Device/System	The test devices consist of the LUX-Dx ICM, Patient and Clinic Mobile Applications, and LATITUDE Clarity Data Management System. The number of devices expected to be used are approximately the same as the number of total enrollment of the subjects in the study.
Study Design	The LUX-Dx PERFORM Study is a prospective, multi-center, single arm, post-market, observational study.
Planned Number of Subjects	Approximately 600 to 827 subjects will be enrolled in the study. This includes approximately 600 subjects participating in the extended Holter monitoring part of the study (Holter study), of which 300 subjects will come from the “Atrial fibrillation (AF) management, Post-AF ablation, or Suspected AF” indication subgroup, and 300 subjects will come from the other two indication subgroups: “Cryptogenic stroke” and “Syncope”.

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Planned Number of Sites /Countries	This study is planned to be conducted at up to 35 sites in the United States to support the required study enrollment. It is possible that sites in Europe or Asia Pacific may join the study upon product approval in those geographies.
Study Objectives	
Primary Effectiveness Objective 1	Characterize the utilization of the remote programming feature
Primary Effectiveness Objective 2	Characterize the performance of the arrhythmia detection algorithms
Primary Safety Endpoint - Acute	ICM System-related Complication-free Rate (CFR) at 30 days post-implant
Primary Safety Endpoint - Chronic	ICM System-related Complication-free Rate (CFR) at 12 months post-implant
Method of Assigning Patients to Treatment	Patient who will be implanted with a BSC LUX-Dx ICM based on labelled indications and meet study-specific eligibility criteria will be considered for enrollment. To be enrolled in the study, subjects must meet all study-specific eligibility criteria and sign the study-specific Informed Consent Form (ICF).
Follow-up Schedule	All subjects must complete the enrollment visit before receiving implantation of the LUX-Dx ICM. Following consent into the study, relevant data including reportable adverse events and ICM device data from the LATITUDE Clarity will be collected during the subject's study participation period. Specifically, participating sites will be requested to review each enrolled subject's electronic medical record (EMR) and communicate with the subject by conducting telephone call/virtual health visit or in-office visit if scheduled per standard of care to the subject at two primary time points (6 months and 12 months post-implant) for relevant adverse events. Each subject's study participation period will be approximately one year or until BSC notifies all sites that data collection is complete.

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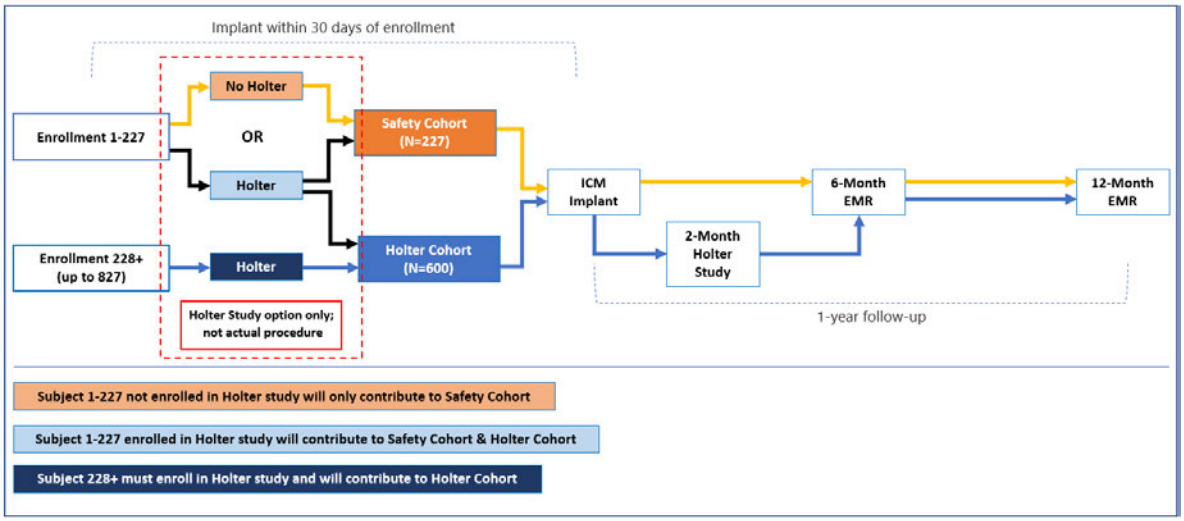
	Additionally, extended Holter monitoring (defined as a monitoring period of 14 days) will be conducted with a subset of subjects at the 2-month in-office visit or remotely by telephone/virtual health visit. To determine which subjects are required to join the Holter study, the following study cohorts are specified: • The first 227 subjects enrolled in the study belong to the "Safety Cohort". The number of subjects is required to fulfill the sample size requirement of the primary safety endpoint. The "Safety Cohort" subjects are not required to participate in the Holter study. • Once the "Safety Cohort" enrollment is completed, all subsequent subjects are required to participate in the Holter study. • All subjects who participate in the Holter study belong to the "Holter Cohort", which is to fulfill the sample size requirement of the primary effectiveness objective 2.
	
Study Duration	The study is expected to last approximately 3.5 years from the first enrollment to study closure.
Participant Duration	The study duration for each enrolled subject is expected to be approximately 12 months.
Inclusion Criteria	• Patient is indicated to be implanted with the LUX-Dx ICM for one of the following reasons (grouped in three "Reason for Monitoring" subgroups):

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	○ Cryptogenic stroke ○ Syncope ○ AF management, Post-AF ablation, or Suspected AF • Patient is willing to enroll and be monitored in LATITUDE Clarity. • Patient is willing and able to be followed remotely via the ICM patient mobile app. • Patient is willing and capable of providing informed consent (which is not to include the use of a legally authorized representative (LAR) for documentation of informed consent) and agrees to participate in all protocol required activities. • Patient is age 18 years or above, or of legal age to give informed consent specific to state and national law. The following inclusion criterion is applicable for patients participating in the Holter study: • Patient can tolerate the adhesive used in the Holter monitoring for an extended period of time.
Exclusion Criteria	• Patient is indicated for implantation of, or is currently implanted with an active implantable cardiac device (e.g., LVAD, ICD, CRT-D, PPM*). • Patient cannot tolerate a subcutaneous, chronically-inserted device due to medical condition. • Patient has a documented life expectancy of less than 12 months (per investigator's discretion). • Patient is known to be pregnant at the time of study enrollment (method of assessment upon investigator's discretion). • Patient is currently enrolled in another clinical study including observational studies/registries, unless prior written approval from BSC is obtained. Mandatory governmental registries are accepted for co-enrollment without approval by BSC. The following exclusion criteria are applicable for patients participating in the Holter study: • Patient has known allergies to the adhesive materials or hydrogel used in the extended Holter monitoring. • Patient has broken, damaged, or irritated skin over the chest area where the extended Holter monitor will be attached.

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	*LVAD: Left Ventricular Assist Device; ICD: Implantable Cardioverter Defibrillator; CRT-D: Cardiac Resynchronization Therapy-Defibrillator; PPM: Permanent Pacemaker
Statistical Methods	
Primary Statistical Hypothesis	There are no primary effectiveness hypotheses but rather primary effectiveness objectives which involve characterizing and summarizing data. The primary safety endpoint - acute hypotheses are: • H_0: ICM system-related complication-free rate at 30 days post-implant $\leq$ 94% • H_A: ICM system-related complication-free rate at 30 days post-implant > 94% The primary safety endpoint - chronic hypotheses are: • H_0: ICM system-related complication-free rate at 12 months post-implant $\leq$ 93% • H_A: ICM system-related complication-free rate at 12 months post-implant > 93%
Statistical Test Method	Primary Effectiveness Objective 1: Remote Programming [redacted] Primary Effectiveness Objective 2: ICM algorithm performance [redacted] Primary Safety Endpoint - Acute: ICM system-related complication-free rate • Kaplan-Meier rate with a one-sided pointwise log-log confidence limit Primary Safety Endpoint - Chronic: ICM system-related complication-free rate

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	• Kaplan-Meier rate with a one-sided pointwise log-log confidence limit
Sample Size Parameters	Approximately 600 to 827 subjects will be enrolled to fulfill the objectives and safety endpoints. Approximately 600 subjects are desired for sufficient data in the Holter study and 227 subjects are needed for the safety endpoints. A total of 227 enrollments are required for the safety endpoint but the first 227 subjects are not required to enroll in the Holter study. Thus, if the first 227 subjects do not enroll in the Holter study then a maximum sample size would be 827. The overall sample size is based on the Holter study and the primary safety endpoint – acute. [redacted]

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3. Table of Contents

3.1. *Table of Figures*

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4. Introduction

4.1. *Background*

Cardiac arrhythmias, especially atrial fibrillation (AF), affect millions of people worldwide. Standard of care methodologies to detect and diagnose these arrhythmias include electrocardiogram (ECG), ambulatory rhythm monitoring (e.g. Holter monitor), mobile cardiac outpatient telemetry (MCOT), and cardiac implantable electronic devices (CIED) with arrhythmia detection and therapeutic capabilities such as pacemakers and defibrillators.[1,2] Non-invasive diagnostic techniques have drawbacks including patient compliance and limited duration of monitoring, while pacemakers and defibrillators are restricted to only those patients meeting indications for therapy (bradycardia and/or tachycardia) once the diagnosis has already been established in most cases.[3-7]

To fill this gap and to aid clinicians in determining the cause of symptoms such as unexplained syncope and palpitations, insertable cardiac monitors (ICMs) that allow for long-term cardiac rhythm monitoring and require a simple subcutaneous implant procedure with a low complication rate have been developed.[8-11] This approach has shown promising results in patients who are at increased risk of cardiac arrhythmias.[12-16]

Boston Scientific (BSC) has developed an ICM system, LUX-DxTM, which is indicated for use in patients that have a known heart condition, are at risk of developing an abnormal heart rhythm, or have symptoms that may suggest a cardiac arrhythmia (e.g. dizziness, palpitations, syncope, chest pain, and/or shortness of breath). The LUX-Dx ICM uses a data management system, LATITUDE Clarity™, which allows clinicians to remotely monitor and program the ICM. In order to transfer the ICM device data to LATITUDE Clarity, the system utilizes the myLUX™ mobile patient app. This allows clinicians to access the device data for analysis to support their evaluation of the clinical status and to adjust the diagnostic programmable features as needed.

4.2. *Study Rationale*

Real-world clinical data for patients implanted due to cryptogenic stroke, suspected AF, syncope, AF management, or post-AF ablation are necessary to understand the usage of remote programming, the performance of arrhythmia detection algorithms of the LUX-Dx ICM, and the safety of the ICM system. This trial's patient population is representative of the majority of the intended recipients of the LUX-Dx ICM. The data collection in the LUX-Dx™ Insertable Cardiac Monitor Remote Programming and Performance Study (LUX-Dx PERFORM) may also be used by BSC for future product enhancements and support future regulatory submissions.

5. LUX-Dx ICM Device/System Description

Refer to Table 5-1 for a summary of the LUX-Dx ICM system components used in the study.

5.1. *LUX-Dx ICM*

The LUX-Dx ICM is a small, leadless electronic device implanted under the skin in the left anterior chest wall. Its primary functions are to monitor, record, and store data related to cardiac arrhythmias. Two electrodes on the body of the device are used to monitor and record the patient's subcutaneous ECG (S-ECG) data when specific arrhythmias (according to the device-programmed settings) are detected, which include pause, bradycardia, tachycardia, AF, and atrial tachyarrhythmias (AT). In addition, the device will record S-ECG data when the patient triggers the device to record via the myLUX patient app. The ICM's memory can store up to 60 minutes of S-ECG recordings. Initial default arrhythmia detection parameters are provided by LATITUDE Clarity according to the Reason for Monitoring. However, these can be configured and adjusted by the clinician according to the subject's clinical indication.

5.2. *Mobile Applications*

There are two mobile applications used to interrogate the LUX-Dx ICM and transmit data from the device to the LATITUDE™ server: a patient-specific app called **myLUX**, and a clinic-specific app called **LUX-Dx Clinic Assistant**. The patient app also allows patients to record and send S-ECGs of symptomatic events to the LATITUDE server. Both apps communicate with the device using Bluetooth Low Energy (BLE) technology, and with the LATITUDE server using a Wi-Fi or cellular connection. Refer to Figure 5-1 for a diagram of the LUX-Dx ICM System.

Figure 5-1: LUX-Dx ICM System Diagram

5.3. *LATITUDE Clarity Data Management System*

LATITUDE Clarity Data Management System consists of a central LATITUDE server and website. LATITUDE Clarity is the website's diagnostics environment that is used to program the LUX-Dx ICM and to review and evaluate clinical data. All remotely transmitted data is sent to the LATITUDE server and is available on the LATITUDE Clarity website to authorized health care providers. Data stored on LATITUDE Clarity during subject's study participation will be used to support analysis of the study objectives.

Table 5-1: BSC LUX-Dx ICM Device and Associated Components

System Component	Description	Model Number
ICM Device	LUX-Dx Insertable Cardiac Monitor (ICM)	M301
Mobile Applications*	myLUX software (patient app)	2925
	LUX-Dx Clinic Assistant software (clinic app)	2935
Server and Website	LATITUDE Clarity Data Management System	7260
Items Included in Package Additional Tools	The following sterile items are included in the package: • Insertable Cardiac Monitor device preloaded in the insertion tool • Incision tool • Sterile pouch	(part of M301)
Additional Tools used during implant, but not packaged with it	• Mobile device** with patient app or clinic app pre-installed • Magnet • Mobile device power adapter with USB cable (as needed)	6259 myLUX 6256 LUX-Dx Clinic Assistant 6386 magnet

*Future mobile or firmware applications may be used when they receive product clearance from regulatory agenc(ies)

**Including future mobile devices when they are available for use in the study

5.4. *Additional Required Medical Equipment and the Associated Procedures*

A commercially approved Holter monitor and its accessories will be provided for the study sites to conduct the 14-day, extended Holter monitoring part of the study (Holter study). The equipment and monitoring service will be provided by an independent Core lab. Refer to Section 10.7 for a description of the Holter study methodology.

6. Study Objectives and Endpoints

The first primary objective of the LUX-Dx PERFORM Study is to characterize the utilization of the remote programming feature of the ICM in a real-world setting. Also, the study will characterize the performance of the arrhythmia detection algorithms based on episodes detected and recorded by the LUX-Dx ICM as well as compared to an extended Holter monitor. Finally, data collected will be used to analyze and characterize ICM system-related safety events. There are two safety endpoint hypotheses in this study. A safety performance goal is established for the ICM system-related complication-free rate at 30 days and at 12 months post-ICM implant, respectively.

7. Study Design

The LUX-Dx PERFORM Study is a multicenter, prospective, single-arm, post-market, observational study.

7.1. *Scale and Duration*

The LUX-Dx PERFORM Study is planned to be conducted at approximately 25 to 35 sites in the US and will enroll approximately 600 to 827 subjects. The final enrollment number is driven by the number of subjects participating in the Holter study. It is possible that study sites from Europe or Asia Pacific may participate upon product approval in those geographies. The number of sites may go up to 35 sites if it is required to sufficiently support the study enrollment completion. Sites may continue to enroll subjects until notified by BSC of enrollment completion. Additional provisions for each site's enrollment are specified in Section 11.2.3.

The first 227 subjects belong to the "Safety Cohort", and must be enrolled to satisfy the sample size required for the safety endpoint analysis. See Section 11.1.5. for detailed discussion on sample size requirements.

The ICM implant procedure must be performed within 30 days following the subject consent. Relevant study data including implant procedure-related data, reportable adverse events, and ICM device data from the LATITUDE Clarity will be collected during the subject's study participation period. Specifically, participating sites will review each enrolled subject's electronic medical record (EMR) and communicate with the subject via telephone calls/virtual health visit or in-office visit that might be part of the standard of care at two primary time points (6 months and 12 months after implant) for relevant adverse events. For the purpose of this study, these follow-up visits do not require subjects' physical presence at the study site. Each subject's study participation period will be approximately one year from the point of device implant or until BSC notifies all sites that data collection is complete.

Defined as the "Holter Cohort", a subset of approximately 600 subjects will wear an extended Holter monitor for a monitoring period of approximately 14 days. This will be performed at the 2-month in-office visit or remotely by telephone call/virtual health visit. The purpose of the Holter cohort is for calculating diagnostic performance of the ICM.

Refer to Figure 7-1 for a diagram of the study design, subject cohort, and flowchart.

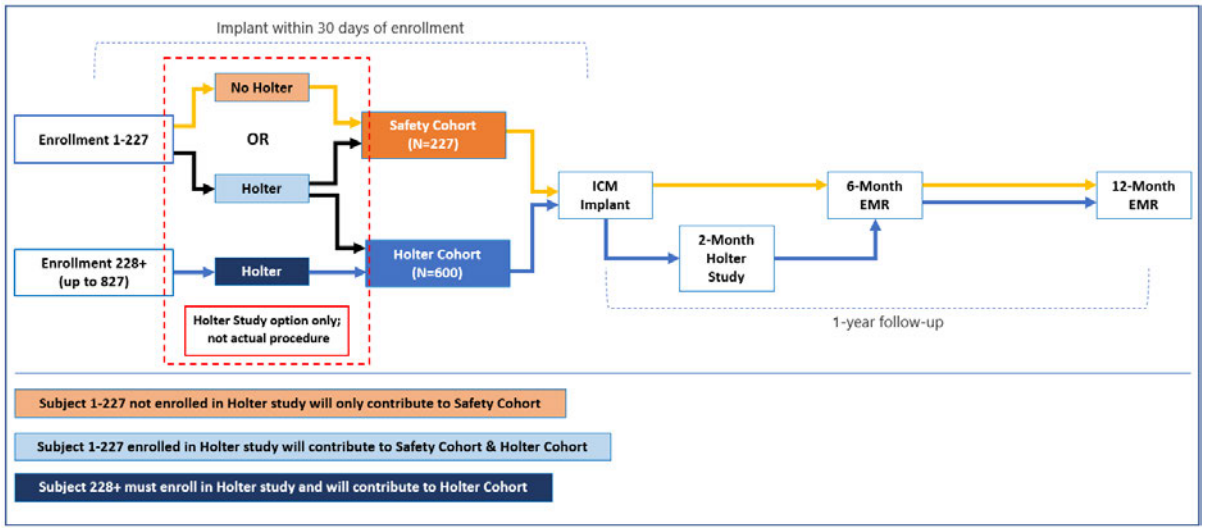

Figure 7-1: Study Design, Subject Cohort, and Flow Diagram

Enrollment is expected to be completed in approximately 30 months; therefore, the total study duration is estimated to be approximately 3-4 years. The total study duration for each implanted subject is approximately 12 months.

7.2. *Treatment Assignment*

Patients who have an indication to be implanted with a LUX-Dx ICM based on the product's labelled indications, and who meet study-specific eligibility criteria will be considered for enrollment. To be enrolled in the study, subjects must meet all study -specific eligibility criteria and sign the study-specific Informed Consent Form (ICF).

There is no randomized treatment assignment in this study. The study is considered "all comers" for patients who are eligible.

7.3. *Justification for the Study Design*

The objective of the LUX-Dx PERFORM Study is to collect data in a clinical setting reflecting real-world usage of the LUX-Dx ICM. Therefore, a prospectively enrolled, observational, post-market study design was determined to be appropriate. Subject enrollment requirements are supported by the following:

- A sample size of 227 subjects will be required to power the first primary safety endpoint analysis (acute endpoint), and 226 subjects will be required to power the second primary safety endpoint (chronic endpoint).
- The Holter study group is expected to enroll approximately 600 subjects, including approximately 300 subjects from the "AF management, Post-AF ablation, or Suspected AF" subgroup, and approximately 300 subjects from the other 2 subgroups ("Syncope" and "Cryptogenic stroke"). The distribution of the device indications is desired to generate at least 100 subjects with a detected AF episode during the Holter

monitoring period. Refer to Section 11.1.2.2 for rationales of the sample size requirement in the Holter study.

Refer to Section 11 for details of overall study sample size discussion.

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects should be selected from the general patient population indicated for ICM implantation per BSC labeled indication and are accessible to the Investigators. The LUX-Dx ICM System is indicated to monitor and record S-ECG for the clinical evaluation and diagnosis of cardiac arrhythmias in patients who have: 1) a known heart condition, 2) are at risk of developing an abnormal heart rhythm, or 3) have symptoms that may suggest a cardiac arrhythmia (e.g. dizziness, palpitations, syncope, chest pain, and/or shortness of breath). The Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility for the study as described in Section 8.2 and 8.3 below.

8.2. *Inclusion Criteria*

Patients who meet all of the following criteria (see Table 8-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criteria (see Section 8.3) are met.

Table 8-1: Inclusion Criteria

Inclusion Criteria	• Patient is indicated to be implanted with the LUX-Dx ICM for one of the following reasons (grouped in three "Reason for Monitoring" subgroups): o Cryptogenic stroke o Syncope o AF management, Post-AF ablation, or Suspected AF • Patient is willing to enroll and be monitored in LATITUDE Clarity. • Patient is willing and able to be followed remotely via the ICM patient mobile app. • Patient is willing and capable of providing informed consent (which is not to include the use of a legally authorized representative (LAR) for documentation of informed consent) and agrees to participate in all protocol required activities. • Patient is age 18 years or above, or of legal age to give informed consent specific to state and national law. The following inclusion criterion is applicable for patients participating in the Holter study: • Patient can tolerate the adhesive used in the Holter monitoring for an extended period of time.

8.3. *Exclusion Criteria*

Patients who meet any one of the following criteria (Table 8-2) may not take part in this clinical study.

Table 8-2: Exclusion Criteria

Exclusion Criteria	• Patient is indicated for implantation of, or is currently implanted with an active implantable cardiac device (e.g., LVAD, ICD, CRT-D, PPM*). • Patient cannot tolerate a subcutaneous, chronically-inserted device due to medical condition. • Patient has a documented life expectancy of less than 12 months (per investigator's discretion). • Patient is known to be pregnant at the time of study enrollment (method of assessment upon investigator's discretion). • Patient is currently enrolled in another clinical study including observational studies/registries, unless prior written approval from BSC is obtained. Mandatory governmental registries are accepted for co-enrollment without approval by BSC. The following exclusion criteria are applicable for patients participating in the Holter study: • Patient has known allergies to the adhesive materials or hydrogel used in the extended Holter monitoring. • Patient has broken, damaged, or irritated skin over the chest area where the extended Holter monitor will be attached. *LVAD: Left Ventricular Assist Device; ICD: Implantable Cardioverter Defibrillator; CRT-D: Cardiac Resynchronization Therapy-Defibrillator; PPM: Permanent Pacemaker

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects will be considered enrolled into the study at the time of study-specific ICF execution. All subject enrollments will be counted against the enrollment ceiling for the study.

9.2. *Enrollment Control*

Approximately 600 to 827 subjects will be enrolled.

9.2.1. Enrollment Control of the "Safety Cohort" Subjects

The first 227 subjects are required to meet the sample size requirement set for the study's primary safety endpoint - acute. These subjects will be asked to participate in the Holter study, but will not be required to join if subject declines.

9.2.2. Enrollment Control of the Holter Study

Enrollment in the Holter study will also be controlled to ensure approximately 300 subjects are from the "AF management, Post-AF ablation, and Suspected AF" subgroup. This sample size is required to satisfy the data requirement for this objective.

It is expected that a total of approximately 600 subjects will be required to participate in the Holter study. BSC may determine that additional subjects will be needed to meet the requirement if data collected are deemed inadequate. In this case, site will continue to enroll Holter subjects until BSC communicates to all sites to stop enrollment.

9.2.3. Enrollment Control at Each Site

No single site may enroll greater than 90 subjects in the study without prior approval from BSC. Additionally, no single site may enroll greater than 34 subjects in the Safety Cohort (the first 227 subjects in the study) without prior approval from BSC.

9.3. *Withdrawal*

All subjects enrolled in the study shall be accounted for and documented including those subjects who withdraw prior to the 12-month electronic medical record (EMR) review. The reason(s) for withdrawal shall be reported on the End of Study Case Report Form (CRF). Reason(s) for withdrawal may include, but are not limited to:

- Subject found not meeting study's eligibility criteria
- Lost to follow-up
- Not able to re-establish device transmission after 90 days despite subject contact
- Subject choice to withdraw consent
- Investigator decision to withdraw the subject
- Subject is classified as Intent or Attempt as per Section 9.5
- The ICM is explanted or permanently disabled with all features programmed off
- Subject implanted with active therapy device (e.g. LVAD, ICD, CRT-D, PPM) even if the ICM remains implanted

9.4. *Lost to Follow-Up*

Any subject without a LATITUDE Clarity device transmission within 90 days prior to each required data collection point may indicate a potential lost to follow-up subject. The investigator or designee shall make efforts to contact the subject in order to re-establish successful LATITUDE Clarity device transmission. Subjects will be classified as lost to follow-up on the End of Study CRF after three documented failed attempts (by either telephone call or certified letter) to contact them are documented in the study file. *Note: the end of study date should be on or after last documented contact attempt*.

9.5. *Subject Status and Classification*

Enrolled subjects will be classified as follows:

Intent refers to a subject who has been enrolled in the study but then does not have local anesthetic administered in preparation for a LUX-Dx ICM implant procedure. The original ICF and enrollment documentation for intent subjects should be maintained in the study file. The Intent subjects must be withdrawn from the study and the End of Study CRF completed. If the Intent subject is withdrawn due to reason of eligibility violation, a protocol deviation is required. There are no follow-up requirements for intent subjects.

Attempt refers to a subject who has been enrolled in the study, has had local anesthetic administered in preparation for the implant procedure of a LUX-Dx ICM, but is not successfully implanted with the LUX-Dx ICM. Attempt subjects must be followed at least 30 days post implant attempt and all reportable adverse events associated with the LUX-Dx ICM or attempted implant procedure must be reported and followed to resolution, or closure of the event with ongoing or chronic status. The safety check attempts must be made between 30 days and 60 days after the attempted implant procedure. These subjects must be withdrawn from the study and the End of Study CRF completed after the resolution of all reportable adverse events and the completion of the safety check.

Implant refers to a subject who has been enrolled in the study and is successfully implanted with the LUX-Dx ICM. These subjects are followed in accordance with the protocol and included in all applicable analyses.

9.6. *End-of-Study Definition*

End of Study occurs when all subjects have been enrolled, implanted, and followed for 12 months. Upon completion of participation in the study, subjects will be followed according to the site's standard of care.

10. Study Methods

10.1. *Data Collection*

The study data collection and follow-up schedule are shown in Table 10-1. Study data collection time-points are initiated from the date of the LUX-Dx ICM implant for each subject. *Note: the 6-month and 12-month EMR reviews do not require in-office visits but instead require the study sites to review a subject's electronic medical record (EMR) and reach the subject by phone/virtual health visit or in-office visit that might be standard of care for applicable study data.* A preliminary list of data collection items is provided in Appendix 26.1.

Table 10-1: Data Collection Schedule (Pre-implant Subject)

Procedure/Assessment	Enrollment	Implant Procedure (day=0) (within 30 days after enrollment)	Data Collection Points/Follow-up Visits	
			2-Month (±30 Days)	6-Month (±30 Days), 12-Month ((±30 Days), End of Study
Informed consent	**X**	**--**	**--**	**--**
Inclusion/ exclusion criteria	**X**	**--**	**--**	**--**
Assessment of pregnancy for women of childbearing potential	**X**	**--**	**--**	**--**
Demographics / physical assessment	**X**	**--**	**--**	**--**
Medical history	**X**	**--**	**--**	**--**
Implant procedure data	**--**	**X**	**--**	**--**
Holter study	**--**	**--**	**X***	**--**
ICM reprogramming	**--**	**Collect for each occurrence†**		
EMR review and phone/virtual health visit or in-office visit per standard of care	**--**	**--**	**--**	**X**
Ongoing AE assessment[1] and protocol deviation	**Collect as it occurs**			

X=Required; X*=Required for approximately 600 subjects; --=Not required; †=Only the first 5 are required to be entered in the database

[1] Reportable adverse events are defined in Section 19.1.

10.2. *Study Candidate Screening and Recruitment*

After the study site receives IRB/EC approval for the LUX-Dx PERFORM Study protocol and ICF, as well as the ATE by BSC, the Investigators may screen patients for inclusion in the study. Study recruitment will rely upon the general pool of ICM -indicated patients.

10.3. *Informed Consent*

The investigator and the designated site staff are responsible for obtaining eligible subject's written informed consent before any study-required procedure and data collection take place.

10.4. *Enrollment Visit*

All subjects who sign the IRB/EC-approved ICF will be considered enrolled in the study. The study site will collect baseline data from the subject's medical record and subject interview as outlined in Table 10-2. The "Reason for Monitoring" at the time of the enrollment will be used to determine which indications subgroup the subject belongs to.

Print any applicable Technical Source Form (TSF) for this visit. Data and source documentation requirements are summarized below in Table 10-2.

Table 10-2: Enrollment Visit Source Documentation

Data Collection	Retention of Original Source Documentation
Informed consent documentation	Study Site
Inclusion/exclusion criteria	Study Site
Assessment of pregnancy for women of childbearing potential	Study Site
Baseline data including: • Demographics • Medical history • Physical assessment of weight and height	Study Site

10.5. *ICM Implant Procedure (within 30 days of Enrollment Visit)*

The ICM implant procedure must occur within 30 days following enrollment. The procedure must be completed by an implanter authorized to perform the LUX-Dx ICM implant, and shall be performed according to the recommended implant technique described in the LUX-Dx ICM User's Manual. The study site will collect data associated with the implant procedure.

To obtain optimal sensing performance, it is strongly recommended to achieve a minimum of 0.2 mV in R-wave amplitude during the implant procedure. If this minimum value is not met, the ICM should be repositioned attempting to achieve a more desirable value before concluding the implant. Document any repositioning attempts in the appropriate CRF. Investigators are asked to follow the most current LUX-Dx ICM User's Manual for requirements or recommendations provided for the implant procedure.

Enrollment in LATITUDE Clarity can be performed prior to, during, or immediately after the implant procedure; however, registration of the LUX-Dx ICM device in LATITUDE Clarity requires the serial number of the ICM device and thus needs be performed after the implant. Device registration in LATITUDE Clarity must be completed within 7 days of the implant procedure. A copy of the LATITUDE Clarity programming report printed within 7 days of implant that displays a completed device set up serves as evidence that device registration is completed as required.

Print any applicable TSF and LATITUDE Clarity programming report (generated within 7 days of device implant). Data and source documentation requirements are summarized below in Table 10-3.

Table 10-3: ICM Implant Procedure Source Documentation

Data Collection	Retention of Original Source Documentation
Implant procedure information including but not limited to: • Device implant procedure time, R-wave amplitude, repositioning attempt, and suturing technique • Implanting facility: in-hospital vs. in-office • Reason for unsuccessful implant	Study Site
Product information: • ICM device details (model/serial, etc.) • Implant tools and accessories used	Study Site
ICM programming information	Study Site
Reportable adverse events (as defined in Section 19.1) and protocol deviations, if applicable	Study Site

10.6. *ICM Reprogramming (throughout the study)*

ICM reprogramming is defined as the modification of any programmable settings after the ICM is considered finally programmed following a successful implant and the subject is discharged from the implanting facility. Reprogramming can be achieved by using the remote programming feature via LATITUDE Clarity or performed during in-office visit. Because there may be many reprogramming attempts made on one subject, for the purpose of this study only the first 5 reprogramming events are required to be entered in the database per subject.

Reprogramming that are performed via the LATITUDE server but with the reprogrammed values not yet confirmed on the subject's ICM device are shown as "pending delivery to device" or similar message on the initial LATITUDE Clarity programming report. It is required that the reprogrammed values be delivered to the subject's device and a programming report be printed documenting the final delivery of the reprogrammed values. If the reprogrammed values continue to stay as "pending delivery to device", the site staff is asked to review the subject's monitoring status on the LATITUDE Clarity website to obtain issues identified by the system. This information will help the site staff troubleshoot and finalize the reprogrammed values, including contacting the subject to resolve connection issues.

The reason for reprogramming, methods of reprogramming (remotely or in-person), and confirmation of reprogramming completion must be reported on the appropriate CRF.

Print any applicable TSF and a copy of LATITUDE Clarity programming report documenting programming information each time that a device reprogramming is performed and successfully completed. Data and source documentation requirements are summarized below in Table 10-4.

Table 10-4: ICM Reprogramming Source Documentation

Data Collection	Retention of Original Source Documentation
ICM programming information following a device reprogramming	Study Site
Reportable adverse events (as defined in Section 19.1) and protocol deviations, if applicable	Study Site

10.7. *2-Month Holter Study Visit (±30 days)*

Approximately 600 subjects are required to complete the Holter study. While in-office visit is preferred for subjects to receive instructions from the study staff for wearing the Holter monitor, subjects may choose to complete this visit via a telephone call or virtual health visit as an alternative. This study procedure is performed at 2 months (±30 days) post-ICM implant.

At this visit, the appropriately trained/delegated study staff will apply the first Holter monitor and instruct the subject on the use of the device during the 14-day monitoring period. In case of by phone/virtual health visit, subject will receive the Holter monitor in the mail and self-apply the Holter monitor per instructions. After the first week the subject is required to remove the first Holter and apply a second Holter. It is highly recommended that the study staff call the subject during the monitoring period to ensure that the subject is applying the Holter monitor properly per instruction and help troubleshoot if there is any issue with the Holter monitor. At the end of the 14-day monitoring period, the subject will send both Holter monitors to the site using a pre-addressed shipping label. The Holter monitor data will be downloaded and transmitted or sent to the independent Core lab by the study staff for data collection. The site staff will clean and sanitize the Holter monitors for future use per site's standard of care methods and applicable labeled instructions provided by the product manual.

To obtain a sufficient number of extended Holter datasets from the "AF management, Post-AF ablation, or Suspected AF" subgroup (approximately 300), BSC will monitor the number of subjects enrolled in the Holter study and may close enrollment to other subgroups in order to achieve the required number of subjects from the "AF management, Post-AF ablation, or Suspected AF" sub-group. This is to ensure an appropriate distribution of the ICM indications. BSC may determine to end the Holter study early before enrollment of 600 subjects are reached, or extend the Holter study to more than 600 subjects mid-study due to inadequate amount of arrhythmia ECG data collected. Study sites will be notified by BSC when the Holter study has completed enrollment.

Print any applicable TSF for this visit. Data and source documentation requirements are summarized below in Table 10-5.

Table 10-5: 2-Month Holter Visit Source Documentation

Data Collection	Retention of Original Source Documentation
Information regarding the extended Holter monitor distribution, return, and data download and transmission	Study Site
Downloaded Holter monitor device raw data	Core lab and BSC
Extended Holter monitoring report and ECG strips	Core lab; a report copy is sent to BSC and Study Site
Reportable adverse events (as defined in Section 19.1) and protocol deviations, if applicable	Study Site

10.8. *6-Month and 12-Month EMR Review (±30 days)*

A review of each implanted subject's EMR must be performed at 6 months (±30 days) and 12 months (±30 days) post-ICM implant. Subjects are not required to visit the study site in-person. Reportable adverse events defined in Section 19.1 shall be collected. To supplement the EMR review, a phone call or virtual health visit to the subject must be attempted and documented to obtain adverse event information that may not be recorded in the EMR. If the subject is seen in-office that might be part of the standard-of care, then a phone call/virtual health visit is not required. It is not a study deviation if the subject cannot be reached by phone or virtual health visit despite attempts. In addition, any ICM reprogramming (to be documented throughout the study duration), arrhythmia diagnoses facilitated by the ICM, and the resulting arrhythmia treatments will be collected on the appropriate CRF. Site staff will confirm successful LATITUDE Clarity device transmission within the last 90 days to determine if the subject may be considered lost to follow-up.

Site is encouraged to perform the EMR review at the time of an in-office standard of care visit, if possible.

Print a copy of initial LATITUDE Clarity programming report to verify the time of the latest device transmission and print the applicable TSF for this visit. Data and source documentation requirements are summarized below in Table 10-6.

Table 10-6: 6- and 12-Month EMR Review Source Documentation

Data Collection	Retention of Original Source Documentation
ICM device transmission information	Study site
Information on arrhythmia diagnoses and related treatments since the LUX--Dx ICM implant	Study site
Reportable adverse events (as defined in Section 19.1) and protocol deviations, if applicable	Study Site

10.9. *LUX-Dx ICM Not in Service, Disabled, or Explanted*

If the LUX-Dx ICM is permanently programmed off and not in service per investigator's decision, disabled due to device issue or malfunction, or explanted for any reason following a successful implant, the reasons for such actions must be recorded on the appropriate CRFs. Subjects with the LUX-Dx ICM disabled, but still implanted will be withdrawn from the study. If disabling of the ICM is a result of an adverse event, these subjects must be followed at least 30 days to assure any associated adverse events are followed to resolution or closure of the event with ongoing or chronic status before withdrawal. The safety check attempts must be made between 30 days and 60 days after the ICM is permanently programmed off or disabled. The withdrawal must occur after the resolution of all reportable adverse events and the completion of the safety check.

All subjects undergoing explant must be followed at least 30 days post explant to ensure any associated adverse events, related to explant or otherwise, are followed to resolution, or closure of the event with ongoing or chronic status. The safety check attempts must be made between 30 days and 60 days after the explant procedure. These subjects must be withdrawn from the study after satisfying the follow-up period of at least 30 days for the safety check.

Print any applicable TSF for this visit. Data and source documentation requirements are summarized below in Table 10-7.

Table 10-7: Device Not in Service, Disabling, and Explant Source Documentation

Data Collection	Retention of Original Source Documentation
Not in service, disabling, and explant information	Study site
Reportable adverse events (as defined in Section 19.1) and protocol deviations, if applicable	Study Site

10.10. *End of Study*

The End of Study CRF must be completed following completion of the subject's 12-month (±30 days) EMR review, upon withdrawal of subject from the study, or upon subject's death. The subject's final status, including confirmation of a successful LATITUDE Clarity device transmission within the last 90 days, will be recorded on the End of Study CRF. There is no in-office visit requirement for this study procedure.

If a subject is experiencing a reportable adverse event at the time of study completion, the study site shall continue following the subject through resolution of the adverse event or closure of the adverse event as chronic or ongoing prior to completing the End of Study CRF.

Upon completion of the study, the subjects will be followed according to the site's standard of care.

10.11. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is

a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

11. Statistical Considerations

11.1. *Objectives*

11.1.1. Primary Effectiveness Objective 1

The primary effectiveness objective 1 is to characterize the utilization of the remote programming feature.

11.1.1.1. Hypotheses

There is no formal hypothesis as this objective is exploratory.

11.1.1.2. Sample Size

There is no formal hypothesis for primary effectiveness objective 1 and no formal sample size requirements for this objective. The overall sample size is driven by the primary effectiveness objective 2 and primary safety endpoint – acute. See section 11.1.5 for more details.

11.1.1.3. Statistical Methods

[redacted]

11.1.2. Primary Effectiveness Objective 2

The primary effectiveness objective 2 is to characterize the performance of arrhythmia detection algorithm.

11.1.2.1. Hypotheses

There is no formal hypothesis as this objective is exploratory.

11.1.2.2. Sample Size

[redacted]

[redacted]

11.1.2.3. Statistical Methods

[redacted]

11.1.3. Primary Safety Endpoint - Acute

The primary safety endpoint – acute is LUX-Dx ICM system-related complication-free rate at 30 days post-implant. The ICM system refers to the LUX-Dx ICM device, mobile apps, and the associated accessories used with the device. See section 11.1.5 for more details.

11.1.3.1. Hypotheses

The primary safety endpoint - acute hypotheses are:

- H_0: ICM system-related complication-free rate at 30 days post-implant $\leq$ 94%
- H_A: ICM system-related complication-free rate at 30 days post-implant > 94%

11.1.3.2. Statistical Methods

The ICM system-related complication-free rate at 30 days post-implant will be calculated using Kaplan-Meier methodology. The 97.5% one-side lower pointwise confidence limit of

the ICM system-related complication-free rate will be calculated via log-log methodology and compared to the performance target of 94%. If the lower confidence limit exceeds 94% then the null hypothesis will be rejected.

The adjudication of the ICM system-related adverse events and complications will be conducted by independent physician reviewer(s).

11.1.3.3. Sample Size

[redacted]

11.1.4. Primary Safety Endpoint - Chronic

The primary safety endpoint – acute is LUX-Dx ICM system-related complication-free rate at 12 months post-implant.

11.1.4.1. Hypotheses

The primary safety endpoint - chronic hypotheses are:

- H_0: ICM system-related complication-free rate at 12 months post-implant $\leq$ 93%
- H_A: ICM system-related complication-free rate at 12 months post-implant > 93%

11.1.4.2. Statistical Methods

The ICM system-related complication-free rate at 12 months post-implant will be calculated using Kaplan-Meier methodology. The 97.5% one-side lower pointwise confidence limit of the ICM system-related complication-free rate will be calculated via log-log methodology and compared to the performance target of 93%. If the lower confidence limit exceeds 93% then the null hypothesis will be rejected.

11.1.4.3. Sample Size

[redacted]

11.1.5. Overall Sample Size

Approximately 600 to 827 subjects will be enrolled to fulfill the objectives and safety endpoints. Approximately 600 subjects are desired for sufficient data in the Holter study for primary effectiveness objective 2, and 227 subjects are needed for the safety endpoints. A total of 227 enrollments are required for the safety endpoint, but the first 227 subjects are not required to enroll in the extended Holter study. Thus, if the first 227 subjects enroll in the Holter study then the minimum sample size would be 600. If none of the first 227 subjects enroll in the Holter then a maximum sample size would be 827.

Primary effectiveness objective 2 sample size details can be found in section 11.1.2.2, and safety endpoint sample size details can be found in section 11.1.3.3.

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

Data from Implant and Attempt subjects will be used for each objective and endpoint as appropriate. Further details will be outlined in the Statistical Analysis Plan.

11.2.2. Control of Systematic Error/Bias

The number of subjects each center can enroll will be capped and poolability of data will be tested across centers to assess heterogeneity. Additionally, the first 227 enrollments for the safety cohort will not be required to enroll in Holter study to avoid subject selection bias.

11.2.3. Number of Subjects per Investigative Site

To avoid any study site effect and bias, no single site will enroll more than 90 subjects of the total enrollments in the study and 34 subjects for the safety endpoint, without prior approval from BSC.

11.3. *Data Analyses*

11.3.1. Interim Analyses

There are no formal interim analyses. Interim analyses may be performed to support publications or regulatory product approval in geographies outside of US. The number of subjects required for the Holter study will be re-estimated during the study using an observed AF incidence rate and data loss rate to obtain approximately 100 subjects with a true AF episode.

11.3.2. Subgroup Analyses

Objectives may be performed in various subgroups including but not limited to:

- Reason for monitoring
- Sex (Male vs. Female)
- Age (< 65 years vs. ≥ 65 years)
- BMI (Obese vs. Overweight vs. Normal)
- History of atrial arrhythmia (All types vs. None)
- Programming Parameters

Further details will be outlined in the Statistical Analysis Plan.

11.3.3. Justification of Pooling

The poolability of data by center will be assessed to determine if there is heterogeneity of data among the different centers. Further details of poolability testing will be outlined in the Statistical Analysis Plan.

11.3.4. Multivariable Analyses

Multivariable analyses will be detailed in the statistical analysis plan.

11.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

12. Health Economics Outcomes

A formal health economics analysis may be completed as part of the LUX-Dx PERFORM Study. This will take into consideration any differences in complication rates and resource utilization. These inputs may be used in health economics analyses performed.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data collected on the Case Report Form (CRF) will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata 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 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 CRF 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 Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to “Read only” after all data is either “Hard Locked” or “Entry Locked”. Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the “Database Locked” or Decommissioned and all database access revoked.

In addition, electronic device data from the ICM system will be recorded using the LATITUDE Clarity data management system. This system was designed to be in compliance with federal regulations pertaining to electronic data. The LATITUDE Clarity Data Management System is secured with access limited to appropriately trained personnel and its data resides on Boston Scientific servers which perform regular backups.

13.2. *Data Retention*

The Principal Investigator (PI) or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The PI or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the PI or his/her designee 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. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Technical Source Forms (TSF)*

A TSF is developed by BSC 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 BSC representative may complete the TSF at the request of the Principal Investigator. The TSF will be reviewed and signed for approval by the Principal Investigator or his/her designee at the end of each procedure.

13.4. *Core Laboratories*

Independent Core lab(s) will be used to provide the extended Holter monitoring product, service, and data analysis. Separate instruction on working with the Core lab and applicable training will be provided.

14. 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, the reviewing IRB/EC, and the regulatory authority, if applicable 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 using the relevant CRF. Sites may also be required to report deviations to the IRB/EC, and the regulatory authority, per local guidelines and national/government regulations.

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

The sponsor will not approve protocol waivers.

15. Device Accountability

The devices and equipment used in this study will be commercially approved in all geographies where the study is being conducted. Any device tracking and accountability will occur per the required local regulations for commercial devices.

16. Compliance

16.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in accordance with post market clinical follow-up guidelines and will follow the applicable sections of ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site ATE, as provided by the sponsor. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

16.2. *Investigator Responsibilities*

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

The PI'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.
- 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.
- 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 that data reported to the sponsor in the CRFs and in all required reports are attributable, legible, timely, original, accurate, and complete.

- 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 reportable events.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain records and control of the device, ensuring that the study device is used only by authorized/designated users and in accordance with this protocol and Instructions For Use.
- 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 IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained and documented in accordance with applicable laws, this protocol and local IRB/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 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 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, 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.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the PI is responsible for providing appropriate training to ensure study staff are competent to perform the tasks they have been delegated. Adequate supervision of the study staff by an investigator is required. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board*

The investigational site will obtain the written and dated approval/favorable opinion of the Institutional Review Board (IRB)/Ethics Committee (EC) for the clinical investigation before recruiting subjects and implementing all subsequent amendments.

A copy of the written IRB/EC approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the ICF will be BSC and IRB/EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

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

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. 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, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

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.

16.4.1. Role of Boston Scientific Representatives

BSC personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, 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.

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

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 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
- Independently collect critical study data
- Enter data in electronic data capture systems or on paper case report forms

16.5. *Insurance*

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

17. Monitoring

Monitoring 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 PI 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 sponsor will put a plan in place to document the specific monitoring requirements.

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 PI and relevant study personnel are available during on-site or remote monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

18.1. *Risks Associated with Participation in the Clinical Study*

This study will enroll patients who are already indicated to receive an ICM per standard of care and meet the study's eligibility criteria. It involves the collection of data via CRF completion and via LATITUDE Clarity, as well as related clinical event data. There are no specific required treatments or therapeutic interventions in this study. There are no other, additional risks of participating beyond what would be expected with standard of care.

A subgroup of subjects (~600) will wear an extended Holter monitor as required by this study. This device is commercially approved in the US and, despite not being mandatory for patients who receive an ICM, is part of the tools available for clinicians to support medical diagnosis and treatment.

18.2. *Risks Related to the Systems Used in the Study according to their Instructions For Use Manuals*

18.2.1 Extended Holter monitor (anticipated adverse events associated with the use of adhesive patches)

- Minor discomfort, skin irritation, reddening, itching, or rash.

18.2.2 LUX-Dx ICM system (anticipated adverse events associated with the implantation of the LUX-Dx ICM)

- Device migration
- Erosion
- Foreign body rejection phenomena
- Formation of hematomas or seromas
- Infection
- Local tissue reaction
- Tissue damage

Refer to the currently available LUX-Dx ICM User's Manual for an updated list of potential adverse events.

18.3. *Possible Interactions with Concomitant Medical Treatments, if applicable*

There are no concomitant medical treatments.

18.4. *Risk Minimization Actions*

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

18.5. *Anticipated Benefits*

Subject who participates in the Holter study may receive additional arrhythmia monitoring in the 14-day monitoring period by wearing the Holter monitor.

There may be no additional benefit to the subject. However, medical science and future patients may benefit from their participation in this post-market study.

18.6. *Risk to Benefit Rationale, if Applicable*

The implantable device systems and accessories used for this clinical study will be commercially available and are considered to be standard of care for patients indicated for the LUX-Dx ICM implants. The risks involved with subject participation in this study are essentially the same as those to the patients not participating in the study.

19. Safety Reporting

19.1. *Reportable Events by Study Site to Boston Scientific*

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

- Serious Adverse Events
- Serious Adverse Device Effects
- Device Related Adverse Events
- Study Procedure Related Adverse Events
- Cardiac Related Adverse Events
- ICM Related Device Deficiencies
- Unanticipated Adverse Device Effects
- Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

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

If it is unclear whether 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.

Any reportable events, experienced by the study subject after informed consent, whether prior to, during, or subsequent to the implant procedure, must be recorded on the CRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 19-1 for AE definitions).

Refer to Instructions For Use for the known risks associated with the commercial device(s).

19.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19-1 . Administrative edits were made on the safety definitions from ISO 14155 and EU 2017/745 for clarification purposes.

Table 19-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *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, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **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 study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either:

Table 19-1: Safety Definitions

Term	Definition
	1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **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) *Ref: ISO 14155* *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) *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) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **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 assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **Note 1 to entry:** This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.

Table 19-1: Safety Definitions

Term	Definition
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

19.3. *Relationship to Device(s)*

An Investigator must assess the relationship of the reportable AE to the device and/or implant procedure. See criteria in Table 19-2:

Table 19-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device, comparator, or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - 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; - 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; - 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); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - 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.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device or comparator, or the relationship with procedures 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 *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 19-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device, comparator, or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - 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); - 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; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - 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.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 19-3. Adverse events must always be reported through the EDC system whenever possible. However, in the case of any issues where alternative methods of reporting is necessary (i.e. the EDC system is not available), the investigator should contact Boston Scientific and provide the relevant adverse event information in a timely manner by using the study-specific safety mailbox: LUXDXPERFORM.safety@bsci.com.

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Serious Health Threat	Complete applicable eCRF/paper form with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study.

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE CRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event • Reporting required through end of study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event	Complete AE CRF page with all available new and updated information.	• Within 3 calendar days after becoming aware of the event or as per local/regional regulations. • Reporting required through end of study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor.
Serious Adverse Device Effects	Complete AE CRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through end of study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency CRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through end of study

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Adverse Event including Adverse Device Effects	Complete AE CRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Within 10 business days after becoming aware of the information. • Reporting required through end of study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

19.5. *Boston Scientific Device Deficiencies*

Device deficiencies will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided to the study site in the event of an ICM explant during study participation. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate CRF.

19.6. *Reporting to Regulatory Authorities/ IRBs/ ECs/ REBs/ Investigators*

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

The PI is responsible for informing the IRB/EC and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

19.7. *Subject Death Reporting*

A subject death during the study must be reported to Boston Scientific as soon as possible and, in any event, within three (3) calendar days of center aware date. The center's IRB/EC must be notified of any deaths in accordance with that center's IRB/EC policies and procedures. Whenever possible, the device should be interrogated and BSC system components (e.g., the device) should be removed intact and returned promptly to BSC RM for analysis.

A detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death may be requested. 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 or not the death was witnessed;
- 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 sub-Investigator signature and date.

Other Source documents may be requested by BSC. BSC Safety representatives will review, at minimum, information regarding subject deaths that are related to ICM system or implant procedure.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study 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, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO) and approved by the site's IRB/EC, or central IRB/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 IRB/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 IRB/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 PI 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 and by the investigator and/or an authorized designee responsible for conducting the informed consent process. 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 subject.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/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 IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

21. Committees

21.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information.The BSC Medical Safety and Safety Trial Operations team include medical professionals with expertise in electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

21.2. *Steering Committee*

A Steering Committee composed of study's Coordinating Principal Investigator(s) and physicians with expertise in ICM technology will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, and first line review and final decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications.

Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission.

21.3. *Independent Medical Reviewers – Arrhythmia Episodes*

An independent group of physician(s) with pertinent expertise will be established for the study. Their responsibility includes reviewing and adjudicating the arrhythmia episodes detected and recorded by the LUX-Dx ICM.

The group will include practitioners of electrophysiology (EP), cardiac device implant, as well as experts with the necessary therapeutic and subject matter expertise to adjudicate the arrhythmia episodes outlined above. Responsibilities, qualifications and procedures are outlined in a charter.

21.4. *Independent Medical Reviewers – Safety Endpoints*

An independent medical review, performed by at least one individual with pertinent expertise, will be performed to review serious adverse events reported by study investigators for adjudication of LUX-Dx ICM system-related complications. The independent medical review will consist of a review of a safety event dossier, which may include copies of subject source documents provided by study sites, for all reported subject death from any cause.

An independent medical reviewer may be a practitioner of EP and/or cardiology or an expert with the necessary therapeutic and subject matter expertise to adjudicate the ICM system-related complications. Responsibilities, qualifications and procedures are outlined in a charter.

22. Suspension or Termination

22.1. *Premature Termination of the Study*

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

22.1.1 Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development/marketing of the device.

22.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/EC Approval*

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

22.3. *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 IRB/EC and regulatory authorities, as applicable, will also be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

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

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

The PI or his/her designee must return all study-related documents and devices, if supplied by BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4. *Criteria for Suspending/Terminating a Study Site*

BSC reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if the enrollment rate is significantly less than projected and the investigator has been given appropriate time to screen and enroll subjects, 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, the IRB/EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

23. Study Registration and Results

23.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

23.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the BSC Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC, and regulatory authorities, as applicable in accordance with the BSC Policy and local requirements.

23.3. *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 may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific 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.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the BSC Data Sharing Policy (https://www.bostonscientific.com/).

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25. Abbreviations and Definitions

25.1. *Abbreviations*

Abbreviations are shown in Table 25-1.

Table 25-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
App	Application
ASADE	Anticipated serious adverse device effect
BSC	Boston Scientific Corporation
CHF	Congestive Heart Failure
CMS	Center for Medicare and Medicaid Services
CRF	Case Report Form

Table 25-1: Abbreviations

Abbreviation/Acronym	Term
CRT-D	Cardiac Resynchronization Therapy-Defibrillator
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICM	Insertable Cardiac Monitor
ID	Identification
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
LVAD	Left Ventricular Assist Device
PA	Pulmonary Artery
PPM	Permanent Pacemaker
PRM	Programmer
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effects
USADE	Unanticipated Serious Adverse Device Effects
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WIRB	Western IRB

25.2. *Definitions*

Terms used in this protocol are defined in Table 25-2.

Table 25-2: Definitions

Term	Definition
Source Data *Ref: ISO 14155*	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation *Note 1 to entry: This includes source data initially recorded in an electronic format.*
Source Document *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document containing source data.

26. Appendices

26.1. *Appendix A: Preliminary Data Collection Items*

Enrollment	Informed consent signed date
	Holter study consent signed date
	Inclusion criteria
	Exclusion criteria
	Indications
	Pregnancy assessment
Subject Classification Status	Subject classification status
Baseline - Demographics	Age
	Sex
	Ethnicity
Baseline - Physical Assessment	Weight
	Height
Baseline - Cardiac Disease History	Heart failure
	NHYA Class, if available
	LVEF value, if available
	Ischemic cardiomyopathy
	Dilated cardiomyopathy
	Idiopathic cardiomyopathy
	Valvular disease
	Valvular surgery
	Thoracic surgery
	Myocardial infarction
	Coronary artery bypass grafting (CABG)
	Atrial arrhythmia: Atrial fibrillation/ Atrial flutter/ Atrial tachycardia
	Ventricular arrhythmia
	Bradyarrhythmia
Baseline - Comorbidities	Hypertension
	Hyperlipidemia
	Diabetes
	Anemia
	Chronic obstructive pulmonary disease
	Hepatic disease
	Cerebrovascular disease
	Peripheral vascular disease
	Pulmonary hypertension
	Renal dysfunction
	Sleep apnea
Implant Procedure Data	Date of implant procedure
	ICM device information
	Mobile application information
	Implant tools and accessories information

	Procedure times
	Suturing technique
	ICM implanting facility
	Confirmation of LATITUDE Clarity enrollment and device registration
	ICM programming information
	Reason for unsuccessful implant
Device Tracking	Information on ICM repositioning
	Information on device Out of Service (explant, disabling, or permanent programmed off)
ICM Reprogramming	Initial programmed value
	Reason for reprogramming
	Method of reprogramming (in-office or remote)
	New programmed value
	Confirmation of completion of the reprogramming
Extended Holter Monitoring (Holter Study)	Holter monitor distribution and return information
	Holter monitor data download and transmission to Core lab information
6-Month and 12-Month EMR Review	Adverse event assessment in EMR
	Adverse event assessment by phone call/virtual health visit/in-office visit to subjects
	Arrhythmia diagnoses and treatment information
	Device transmission information
End of Study	Subject status
	If withdrawn, reason
	Device transmission information
	If lost to follow-up, information on attempts to locate subject
	Death information
Ongoing Data Collection	Reporting of adverse event/device deficiency
	Reporting of protocol deviation