Clinical Protocol for the BIO-CONDUCT Study

BIO-CONDUCT

BIOTRONIK Conduction System Pacing with the Solia Lead

IDE #G210349

NCT05251363

10-AUG-2022

BIOTRONIK, Inc.

6024 Jean Road

Lake Oswego, Oregon 97035

This document contains confidential information for use only by investigators participating in the clinical study. Therefore, this document should be maintained in a secure location and should not be copied or made available for review by any unauthorized personnel.

Table of Contents

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Table of Tables

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Table of Figures

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

BIO-CONDUCT Study

Protocol Signature Page

The signature below constitutes the receipt and review of the BIO-CONDUCT Study protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH GCP guidelines.

Principal Investigator:

_____
Name (please print)

_____ _____
Signature Date

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Protocol Summary

Title	BIO-CONDUCT Study BIOTRONIK Conduction System Pacing with the Solia Lead
Purpose	Demonstrate the safety and effectiveness of the BIOTRONIK Solia S pacing lead when implanted in the left bundle branch (LBB) area
Design	Prospective, non-randomized, multi-center, investigational device exemption (IDE) clinical study
Study Device	Solia S pacing lead implanted or attempted to be implanted in the LBB area The Solia S pacing lead is market-released in the U.S. This study will occur under an IDE as Solia S does not currently have labelling for sensing and pacing in the left bundle branch area. The term "Solia S LBB lead" in being used in this protocol to refer to the Solia S lead implanted in the LBB area vs. implanted in other areas (e.g. right atrium) and is not intended as a name change for the Solia S lead.
Subject Population	Candidates for permanent pacemaker implantation
Study Size	Up to 260 evaluable subjects enrolled at up to 25 sites in the U.S.
Follow-up Duration	Each subject will be followed for 12 months
Primary Endpoints	1. Safety: Serious adverse device effect (SADE)-free rate through 3 months post-implant 2. Efficacy: Implant success is defined as successful placement of the Solia S lead in the LBB area* with a pacing threshold of less than or equal to 2.5 V @ 0.4 ms and a mean sensing value of greater than or equal to 2.0 mV in the final lead position. *Per criteria in Section 2.1.1.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Secondary Endpoints	1. Quality of Life (QOL) from baseline through 12 Months Post-Implant 2. SADE-free rate for Solia S LBB lead through 6- and 12-months post-implant 3. Solia S LBB lead pacing threshold at 3-, 6-, and 12-month follow-up visits 4. Solia S LBB lead R-wave sensed amplitude at 3-, 6-, and 12-month follow-up visits 5. Solia S LBB lead pacing impedance at 3-, 6-, and 12-month follow-up visits
Inclusion Criteria	• Patient is a candidate for implantation of a BIOTRONIK pacemaker system, per standard guidelines. Single chamber, dual chamber, and CRT-P systems are allowed. • Patient has an implant planned to utilize left bundle branch area pacing within 30 days of consent • Patient is able to understand the nature of the study and provide written informed consent • Patient is available for follow-up visits on a regular basis for the expected duration of follow-up • Patient accepts Home Monitoring® concept • Patient age is greater than or equal to 18 years at time of consent
Exclusion Criteria	• Patient meets a standard contraindication for pacemaker system implant • Patient is currently implanted with a pacemaker or ICD device • Patient has had a previous unsuccessful attempt to place a lead in the LBB area • Patient has planned cardiac surgical procedures or interventional measures within 3 months after implant • Patient is expected to receive a heart transplant within 12 months • Patient life expectancy less than 12 months • Patient has the presence of another life-threatening, underlying illness separate from their cardiac disorder • Patient reports pregnancy at the time of enrollment • Patient is enrolled in any other investigational cardiac clinical study during the course of the study

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

National Principal Investigator	Larry A. Chinitz, MD, FACC, FHRS Director, Cardiac Electrophysiology and the NYU Heart Rhythm Center NYU Heart Rhythm Center 403 East 34th Street, 4th floor New York, NY 10016
Clinical Events Committee Chair	To be determined
Electronic Data Capture Vendor	Mednet Solutions, Inc. 601 Carlson Parkway, Suite 250 Minnetonka, Minnesota 55305
Sponsor	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035 Referred to as "BIOTRONIK" for the remainder of this protocol. For technical assistance 24 hours a day, call: 1-800-547-0394

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

1 Introduction

1.1 Study Overview

This is a multi-center, prospective, non-randomized clinical investigation being conducted to document the clinical experience of the Solia S pacing lead as required by the FDA to satisfy requirements for labelling for use in left bundle branch area pacing (LBBAP). This clinical investigation is designed to enroll up to 260 subjects who will be followed for at least 12 months post-implant at up to 25 clinical study sites within the United States (U.S.).

The Solia S pacing leads are legally marketed in the U.S. This study will occur under an IDE as Solia S does not currently have labelling for sensing and pacing in the LBB area. All other devices utilized in conjunction with this study are U.S. market-released and will be prescribed by physicians according to approved indications for use.

BIOTRONIK intends to pool this prospective study data with prospectively collected data from other sources where Solia S has been implanted in the LBB area.

1.2 Background

Permanent cardiac pacing has been utilized for treatment in patients with sick sinus syndrome (SSS) and high degree AV block. Right ventricular pacing (RVP), has been the standard therapy option for individuals requiring ventricular pacing support due to its accessibility, as well as being stable and well tolerated (De Cock CC et al. 2003; Zhang S et al. 2021). However, studies have demonstrated that long-term RVP has been associated with an increased risk of pacing-induced cardiomyopathy, atrial fibrillation, heart failure hospitalization, and mortality (Wilkoff BL et al. 2002; Sweeney MO et al. 2003; Zhang S et al. 2021). Bansal R et al. (2019) showed that RVP led to pacemaker-induced cardiomyopathy in 13.8% of subjects after a mean follow-up of 14.5 months. These potential effects of RVP are likely due a high burden of RVP and ventricular dyssynchrony. Due to these potential risks, the search has continued to find another location for ventricular pacing to reduce these effects.

Conduction system pacing (CSP) includes both His bundle pacing (HBP) and left bundle branch area pacing (LBBAP) and over time these areas have emerged as potential new locations for ventricular pacing. Both areas have been proposed as more physiologic alternatives to RVP because they more directly engage a patient's specialized cardiac conduction system (Deshmukh P et al. 2000; Vijayaraman P et al. 2017). Between 1995 and 1997, Deshmukh P et al. (2000) began researching pacing in the His bundle area in a small series of patients. Since then HBP has continued to be studied and results have demonstrated that HBP is both feasible and safe, as well as being associated with reduction in a combined endpoint of death and heart failure hospitalization compared to RVP (Abdelrahman M et al. 2018; Vijayaraman P et al. 2018; Sharma P et al. 2015). The majority of HBP implants have been performed using a lumenless exposed screw lead. Early success rates for HBP were around 65% and with increased implant experience and improved guide tools, success rates have improved to 80-90% (Deshmukh P et al. 2000; Sharma P et al. 2018; Vijayaraman P et al. 2018; Su L et al. 2021). Although HBP has been deemed a desirable site for

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

CSP, success rates do vary and placement can be difficult to achieve as practitioners must attempt to place the lead in a relatively small area. Another drawback to HBP is that it has been associated with elevated pacing capture thresholds, as well as a longer implant time, lower R wave amplitude, and higher pacing lead reintervention rates (Vijayaraman P et al. 2018; Sharma P et al. 2018; Zhang S et al. 2021; Jastrzebski M et al. 2018; Keene D et al. 2019; Zanon F et al. 2018). While HBP has a greater body of research over the years, there are still shortcomings with this potential pacing therapy location which has led to a continued effort to explore additional physiologic ventricular pacing options.

More recently there has been a shift to focus on LBBAP due to higher probabilities of success while maintaining the benefit of physiological pacing. An early case report of LBBAP was published in 2017 by Huang W et al. and found improvements in cardiac function. Since then, further studies have been conducted to demonstrate feasibility and safety in this new novel pacing strategy with implant success rates ranging between 87.9% and 97.8% (Zhang S et al. 2021; Su et al. 2021). In total, clinical study results have been published on over 1,750 LBBAP implants. Data has demonstrated lower threshold and narrow paced QRS duration, as well as a reduction in heart failure hospitalizations compared to RVP (Chen K et al. 2019; Zhang S et al. 2021; Su L et al. 2021).

Relative to HBP, LBBAP has demonstrated a greater implant success as it affords the practitioner a larger target area for lead placement and more favorable pacing thresholds and sensing values (Padala SK et al. 2020, De Pooter J 2020). LBBAP captures the His-Purkinje system more distally compared with HBP and requires the lead to be screwed transeptally toward the left side of the interventricular septum (Huang W et al. 2019). Another advantage of LBBAP is that the lead is in close proximity to the ventricular septal myocardium so it can provide backup septal pacing in case of loss of LBB capture if more distal conduction system disease develops (Su L et al. 2021). In an observational registry of 703 patients, LBBAP demonstrated narrower QRS complexes, as well as lower rate of mortality, heart failure hospitalization, or upgrade to biventricular pacing as compared to RVP (Sharma P et al. 2021).

While LBBAP primarily activates the left bundle branch, studies have demonstrated that LBBAP can achieve comparable LV activation and synchrony parameters to HBP (Strocchi M et al. 2020). Additionally, it has been shown that when compared to RV septal pacing, LBBAP maintained better left ventricular mechanical synchrony similar to that of native conduction (Cai B et al. 2020). In Zhang S et al. (2021), authors felt that perhaps the decrease in heart failure hospitalization and atrial fibrillation post-pacemaker implant could be due to the maintenance of ventricular synchrony. Myocardial septal capture and retrograde conduction from the left bundle to the right bundle appear to minimize the possible loss of RV synchrony during LBBAP (Cano Ó et al. 2021). In looking at cardiac resynchronization therapy, Su L et al. (2021) found that for patients with LBBB during intrinsic conduction, QRS width was significantly reduced indicating successful cardiac resynchronization, similar to results seen with successful biventricular pacing. In addition, it was noted that left ventricular ejection fraction (LVEF) and LV end-diastolic dimension improved

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

suggesting greater improvement in LV function and possible reverse ventricular remodeling.

Recently De Pooter J et al. (2020) demonstrated LBBAP using a stylet-driven pacing lead (Solia S, BIOTRONIK, SE & Co. KG) was feasible and yielded comparable success to lumenless leads. LBBAP pacing thresholds were low and comparable between the stylet-driven and lumenless leads.

As conduction system pacing methodologies continue to evolve, more information on the safety and efficacy of leads implanted to support these pacing modalities is needed.

1.3 Rationale for the Study Design

A prospective, single-arm study design has been proposed for this study as the Solia S leads are market-released in the U.S. and the study population and key endpoints are well-defined.

The Solia S leads received FDA approval on June 8, 2016 as a result of the Siello Clinical Study. The leads studied as Siello are marketed under the name Solia S ProMRI in the U.S. The Solia S lead is also currently being utilized in the BIO|MASTER clinical study along with the Selectra 3D guide catheter to achieve CSP. A summary of these studies is below.

In addition, two publications summarizing results of clinical trials utilizing Solia S in LBBAP are included below.

1.3.1 Siello Clinical Study

The safety and effectiveness of the Solia S lead (alternative name for the Siello family of leads) when used for atrial or ventricular pacing was demonstrated in the Siello Clinical Study. In the pre-market phase of the study, a total of 1515 subjects were implanted (or attempted to be implanted) between March 13, 2013 and April 3, 2015 with 2767 Siello S leads (1280 atrial, 1487 ventricular) at 60 US investigational centers, with a cumulative implant duration of 1240.5 years. Mean subject age was 74.3 years, and 53.1% of subjects were male. The most common primary reasons for implant were sinus node dysfunction (65.4%) and acquired atrioventricular block in adults (29.8%). Siello S lead implant was attempted but not successful in one subject.

When used for atrial pacing, the complication free-rate at 12 months post-implant was 100% (450/450), 95% CI (99.2%, 100%). The complication free-rate at 12 months was 99.62% (523/525), 95% CI (98.6%, 100%) for leads placed in the ventricle. Pacing thresholds were low and stable from implant through 18 months post-implant at 0.74 ± 0.30 V at 0.4 or 0.5 ms for ventricular leads and 0.83 ± 0.36 V at 0.4 or 0.5 ms for atrial leads. Sensing was also stable with a mean of 12.25 ± 4.56 mV for the ventricle and 3.56 ± 1.90 mV for the atrium through-out follow-up.

1.3.2 BIO|MASTER.Selectra 3D

The BIO|MASTER.Selectra 3D study is a multicenter, international, prospective, open, non-controlled, non-randomized clinical study to confirm safety, performance and

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

handling of Selectra 3D, assessing also the performance of the system (Solia S, Enitra 8) implanted with Selectra 3D. This study is being conducted outside of the U.S. and is sponsored by BIOTRONIK SE & Co. KG (Berlin, Germany). The study subject population is comprised of patients with an indication for pacemaker or CRT-P therapy according to standard clinical guidelines. The primary endpoint is Selectra 3D-related SADE-free rate until 7 days after implantation. The secondary endpoints are successful implantation rate, appropriate sensing and pacing of Solia S, SADE-free rate of Solia S until the 6-month follow-up, and the SADE-free rate of Solia S until the 12-month follow-up. The expected overall study duration is October 2020 – September 2022. The visit schedule will include enrollment, implantation, pre-hospital discharge, 3 months, 6 months and 12 months post-implant follow-ups. It is anticipated that data from subjects in this study with a successful LBB area lead implant with Solia S may be eligible to pool with results from the BIO-CONDUCT study.

1.3.3 Published Results with Solia

De Pooter J et al., 2020 explored the feasibility, safety, and pacing characteristics of LBBAP using stylet-driven leads (SDLs) with an extendable helix design. Patients in which LBBAP was attempted for bradycardia or heart failure pacing indications were prospectively enrolled. LBBAP was attempted with two different systems: a fixed helix lumenless lead (LLL) and an extendable helix lead (SDL; Solia S60, BIOTRONIK SE & Co. KG). Patients were allocated to either SDL or LLL LBBAP in a nonrandomized way and based on manufacturer preference of the referring cardiologist and availability of leads and implanting tools.

The study enrolled 50 patients (mean age: 70 ± 14 years, 44% females). LBBAP with SDL was successful in 20/23 (87%) patients compared with 24/27 (89%) of patients in the LLL group ($p = 0.834$). Screw attempts, screw implant depth, procedural, and fluoroscopy times were comparable among both groups. Acute LBBAP thresholds were low and comparable between SDL and LLL (0.5 ± 0.15 V vs. 0.4 ± 0.17 V, $p = 0.251$). Pacing thresholds remained low at 3 ± 2.1 months of follow up in both groups and no lead revisions were necessary. Postprocedural echocardiography revealed a septal coronary artery fistula in one patient with SDL LBBAP.

The authors concluded that LBBAP using stylet-driven pacing leads is feasible and yields comparable implant success to LBBAP with LLLs. LBBAP thresholds are low and comparable with both types of leads.

Gillis K et al., 2021 aimed to demonstrate that continuous uninterrupted unipolar pacing from an inserted lead stylet (LS) is feasible and facilitates LBBAP implantation. Thirty patients (mean age 76 ± 14 years) were implanted with stylet-driven pacing lead (Solia S). In 10 patients (validation-group) conventional, interrupted implantation was performed, with comparison of unipolar pacing characteristics between LS and connector-pin (CP)-pacing after each rotation step. In 20 patients (feasibility-group) performance and safety of uninterrupted implantation during continuous pacing from the LS were analyzed.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

In the validation-group, LS and CP-pacing impedances were highly correlated (R2=0.95, p<0.0001, bias 12±37). Pacing characteristics from LS and CP showed comparable sensed electrograms and paced QRS morphologies. In the feasibility-group, continuous LS-pacing allowed beat-to-beat monitoring of impedance and QRS morphology to guide implantation. This resulted in successful LBBAP in all patients, after a mean of 1 attempt, with mean threshold of 0.81 ± 0.4V, median sensing of 6.5mV (IQR 4.4-9.5] and mean impedance of 624 ± 101. The median paced QRS duration was 120ms [(IQR 112-152ms) and median pLVAT was 73ms (IQR 68-80.5ms]. No septal perforation occurred in any patient.

The results demonstrated that unipolar pacing from the LS allows accurate determination of pacing impedance and generates similar paced QRS morphologies and equal sensed electrograms, compared to CP pacing. Continuous LS pacing allows real-time monitoring of impedance and paced QRS morphology, which facilitates a safe and successful LBB area pacing lead implantation.

1.4 Device Description

1.4.1 Solia S Lead

The study device used in this clinical investigation is the Solia S ProMRI® Pacing Lead, referred to as Solia S in this protocol. The BIOTRONIK Solia S transvenous, steroid-eluting, active fixation endocardial lead family is designed for permanent pacing and sensing. Active fixation pacing leads with a bipolar (BP) IS1 connector configuration are designed for use in conjunction with implantable pulse generators with IS-1 compatible headers. The leads may be used with single- or dual-chamber pulse generators, dual chamber ICDs, CRT-P and CRT-D-devices.

Solia S leads feature an electrically active extendable/retractable fixation helix for use in lead placement. The helix is extended and retracted by rotating the connector pin with a fixation tool. Both the fixation helix and ring electrode are comprised of a platinum/iridium alloy base with a fractal iridium surface. The fractal surface of the lead electrodes creates a larger effective surface area, as a result maximizes the myocardial interface, which is a major factor in determining a lead's sensing characteristics. All leads are multi-filar and insulated with medical grade silicone.

The distal tip of the Solia S lead consists of a steroid-eluting collar, containing 0.85 mg of dexamethasone acetate (DXA). Upon exposure to body fluids, the steroid elutes from the collar into the body tissue by diffusion. Release of the steroid is intended to decrease the inflammatory response at the contact site between the lead tip and the endocardium, thereby decreasing the elevated pacing thresholds of the endocardial lead that often occur after lead implantation.

Solia S leads have straight distal ends (Solia S xx) and are intended for placement in either the right atrium or right ventricle. The "xx" represents the lead length in centimeters. The Solia S leads are available in the following configurations for this study: Solia S 53 and Solia S 60. Magnetic resonance imaging (MRI) scanning conditions are shown in Table 1.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

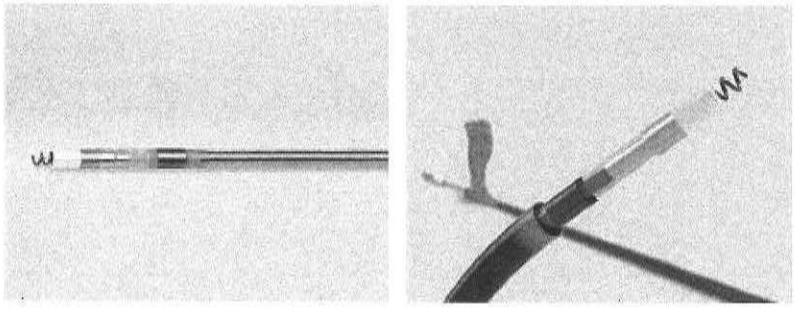

Figure 1: Solia S Lead and Selectra 3D Guide Catheter

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Table 1: Magnetic Resonance Imaging (MRI) Scanning Conditions

MRI Safety Information

A person implanted with Solia S ProMRI ® may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	Solia S ProMRI ®
Static Magnetic Field Strength (B_0)	1.5T or 3.0T
Maximum Spatial Field Gradient	30 T/m
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	Volume Transmit Coil; Local Volume Transmit Coil limited to head or extremities
RF Receive Coil Type	There are no Receive Coil restrictions
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body average SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact

1.4.2 Selectra 3D Guide Catheter

Selectra 3D Guide Catheters facilitate access to the venous system for suitable leads and EP catheters. Selectra 3D is an optional tool that may be used to support the placement of the Solia S pacing lead in the heart chambers, including conduction system pacing locations and may be utilized at the discretion of the implanting physician. In conjunction with the Selectra accessory kit, Selectra guiding catheters are used to facilitate lead implantation in the heart chambers or in the coronary veins via the coronary sinus. The individually available guiding catheters with a nominal inner diameter of 7.3 French and outer diameter of 8.7 French can only be used in combination with the accessory kit of the Selectra lead introducer system.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

1.4.3 Edora 8 Pacemakers

Edora 8 pacemakers are BIOTRONIK's state-of-the-art pacing system, providing wandless telemetry communication, intended to simplify implantation and follow-up procedures. The pacemakers provide pacing support by a sophisticated diagnostic set and a variety of rate-adaptive and non-rate adaptive pacing modes. Rate-adaptative pacing is achieved through programming of either the unique principle of closed-loop stimulation (CLS) or by motion-based pacing via a capacitive accelerometer.

The Edora family of pacemakers is comprised of single or dual chamber pacing systems and CRT-P devices. The devices are designed and recommended for use with unipolar or bipolar pacing leads having IS-1 compatible connectors. The QP model of the CRT-P device uses an IS4 lead for the left ventricle.

1.4.4 BIOTRONIK Home Monitoring®

All BIOTRONIK pacemakers, ICD and CRT-D devices can be used with the BIOTRONIK Home Monitoring® system. The Home Monitoring® system enables wireless automatic transmission of information about a patient's cardiac status from the implanted device to the physician remotely. Home Monitoring® can be used to provide the physician with advance reports from the implanted device and process them into a graphical and tabular format that is accessible via the internet platform Home Monitoring Service Center (HMSC). This information helps the physician optimize the therapy process, as it allows the patient to be scheduled for additional clinical appointments between regular follow-up visits if necessary.

1. Communication starts with the implant, which activates a very low power RF transmitter circuitry integrated within the pulse generator.

2. The patient's implant sends cardiac and device information to the patient's CardioMessenger®. The patient's CardioMessenger® device functions like a cellular phone and transmits the messages received from the implant to the HMSC platform via the cellular phone network.

3. The BIOTRONIK HMSC receives incoming data and generates a customized summary which is available to the physician online via secure Internet. The physician may also receive notifications via short messaging system (SMS) or email when a message from the patient's implant has transmitted to the HMSC.

Figure 2: BIOTRONIK Home Monitoring®

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

In addition, the devices provide the ability to schedule remote follow-up appointments via the Home Monitoring Service Center.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

2 Study Design

In this clinical study protocol, safety and effectiveness data will be collected and evaluated for the Solia S pacing leads placed in the LBB area. This study will enroll up to 260 evaluable subjects at up to 25 clinical study sites in the U.S.

Subjects eligible for the study are candidates for implantation of a BIOTRONIK pulse generator system with no prior failed attempt at LBB area lead placement. Prior to enrollment, eligible subjects will be identified and will provide written informed consent. Following their implant, subjects will be seen either in-office or remotely via Home Monitoring device check including a remote review of adverse events at 3, 6, and 12 months.

BIOTRONIK plans to pool data with other prospectively collected data sources to supplement the LBB area pacing population to achieve the sample size of 260 subjects with 3 months of follow-up needed for the primary endpoint analysis. The data collected from other sources would need to be sufficiently similar to the LBB area pacing study data collection required for primary endpoint analysis to allow pooling of the data. At least 50% of the subjects included in the analysis will be enrolled at US sites.

The term "Solia S LBB lead" is being used in this protocol to refer to the Solia S lead implanted in the LBB area vs. implanted in other areas (e.g. right atrium) and is not intended as a name change for the Solia S lead.

2.1 Study Endpoints

The objective of this clinical investigation is to evaluate the safety and effectiveness of BIOTRONIK Solia S pacing lead implanted in the LBB area.

2.1.1 Primary Endpoints

Primary Endpoint 1: Serious adverse device effect (SADE)-free rate through 3 months post-implant

The purpose of primary endpoint 1 is to evaluate the overall incidence of serious Solia S LBB lead related adverse device effects and serious implant procedure events related to the Solia S LBB lead that occur through 3 months post-implant. The parameter of interest is the Solia S LBB lead complication-free rate per subject, which will be calculated as the number of subjects without one or more complications divided by the total number of study subjects successfully enrolled and subjects undergoing an unsuccessful implant attempt who have a qualifying primary safety endpoint event in percent.

Primary Endpoint 2: Implant success

The purpose of primary endpoint 2 is to evaluate the implant success rate of the Solia S lead in the LBB area. Implant success is defined as successful placement in the LBB area with a pacing threshold of less than or equal to 2.5 V at 0.4 ms and a mean sensing value of greater than or equal to 2.0 mV in the final lead position. Evaluation of the mean sensing value is not required for patients that are pacing dependent.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

For the BIO-CONDUCT study, successful placement in the LBB area is defined as: a) presence of two or more of the criteria listed below as determined and documented by the investigator, with b) at least one of Criterion #1 or #2 being met. (Huang W et al. 2019, Vijayaraman et al. 2021, De Pooter et al. 2020, Wu et al. 2021):

1. Paced QRS morphology that presents with a right bundle branch block (RBBB) pattern
2. Peak LV activation time (stimulus to peak of the R wave in leads V4 to V6) of < 90ms at high and low-output pacing
3. Presence of LBB potentials (LBB-V intervals of 15 to 35ms)
4. Demonstration of output-dependent non-selective LBBAP and selective LBBAP at near threshold outputs

The parameter of interest is the percentage of subjects with Solia S placed successfully in the LBB area with a threshold less than or equal to 2.5 V at 0.4 ms and mean sensing value of greater than or equal to 2.0 mV calculated by the number of subjects who meet that criteria divided by the total number of consented study subjects in whom an implant of Solia S in the LBB area was attempted.

2.1.2 Secondary Endpoints

The following secondary endpoints will be evaluated during this clinical investigation:

1. Quality of Life (QOL) from baseline through 12 Months Post-Implant

The purpose of secondary endpoint 1 is to evaluate the improvement in QOL for subjects with the Solia S lead implanted in the left bundle branch (LBB) area. The parameter of interest is the change in the physical function SF-36 (36-Item Short Form Health Survey) QOL scale from pre-implant baseline to 12 months post-implant, which will be calculated as the mean change from baseline for all subjects that complete both the baseline QOL and 12-month QOL questionnaire. Only subjects from the US prospectively enrolled cohort with successful placement of the Solia S lead in the LBB area and with evaluable QOL paired baseline and 12-month measurements will be analyzed.

Descriptive analysis will be performed for the following secondary endpoints:

2. SADE-free rate for Solia S LBB lead through 6- and 12-months post-implant
3. Solia S LBB lead pacing threshold at 3-, 6-, and 12-month follow-up visits
4. Solia S LBB lead R-wave sensed amplitude at 3-, 6-, 12-month follow-up visits
5. Solia S LBB lead pacing impedance at 3-, 6-, 12-month follow-up visits

2.1.3 Additional Data of Interest

Additional information will be collected to characterize the study population, implanted system, and progress of the clinical investigation. Specifically, further data of interest will include:

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

- Demographics, including age, sex at birth, race and ethnicity, weight, height, pacemaker indication, New York Heart Association (NYHA) class (if available), left ventricular ejection fraction (LVEF) (if available), pre-procedure echocardiogram values (if performed routinely)
- Medical history, including cardiac history and comorbidities
- Cardiovascular medications at implant
- ECG characteristics such as intrinsic QRS duration pre-LBB implant attempt and paced QRS duration post-LBB implant attempt
- Implanted device information for pulse generator and all leads
- Solia S LBB lead measurements at implant and required study follow-up visits, including pacing threshold, R-wave sensing, and pacing impedance, and selective vs. non-selective capture for the Solia S LBB lead (if available)
- Implant procedure information, including handling of lead, utilization of guide catheter, mapping system, and selective vs. non-selective capture for the Solia S LBB lead, etc.
- Device programming and Home Monitoring transmission success
- Adverse events related to implant procedure, lead delivery system, pulse generator, or leads
- Reason for inability to place or achieve capture with Solia S lead in LBB area (if applicable)
- Revisions to implanted system, including reason for revision
- Results from returned product analysis
- Compliance to protocol requirements and study visit schedule Change in QOL scales from pre-implant baseline to the 3-, 6-, and 12-month follow-up for scale changes not evaluated in secondary endpoint 1

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

2.2 Subject Status

Table 2: Subject Status Definitions

Subject Status	Definition
Provisionally Enrolled	Subject has provided written informed consent prior to implant, but subject has not yet been implanted Provisionally enrolled subjects will be implanted and enrolled or exited as a screen failure or unsuccessful attempt.
Screen Failure	Subject has signed consent, but in the time between signing consent and implant attempt it was identified the subject does not meet all inclusion/exclusion criteria OR Subject consented, but exited prior to implant, or does not undergo an implant attempt with a Solia S lead in the LBB area within 30 days of signing consent. An implant attempt in the LBB area is defined as the Solia S lead coming into contact with subject's ventricular septum with the intent to place the Solia S lead in the LBB area.
Unsuccessful Implant Attempt	Subjects with an attempted but unsuccessful implant of the Solia S in the LBB area as defined by criteria in Section 2.1.1 will be followed in a 30-day safety registry prior to being exited from the study. Implant attempt is provided in the Screen Failure definition above.
Enrolled	Subject has met all inclusion and none of the exclusion criteria, provided written informed consent, and was successfully implanted with a Solia S in the LBB area and a BIOTRONIK pacemaker.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

3 Protocol Requirements

3.1 Subject Population

The investigator is responsible for screening all potential patients and selecting those who are appropriate for study inclusion. The patients selected for participation should be from the investigator's general patient population according to the inclusion and exclusion criteria described in Sections 3.1.3 and 3.1.4.

3.1.1 Indications

The BIOTRONIK Solia S lead is a 5.6 French (6F introducer), transvenous, steroid-eluting (0.85 mg DXA), bipolar, IS-1 compatible, active fixation lead intended for permanent sensing and pacing in either the right atrium or right ventricle when used with a compatible pulse generators with IS-1 headers. The leads may be used with single or dual chamber pacing systems, dual chamber ICDs, CRT-P and CRT-D.

This study will evaluate the safety and efficacy of a proposed additional indication of the Solia S lead intended for permanent sensing and pacing in the LBB area as an alternative to right ventricular pacing and used with single or dual chamber pacing systems and CRT-P.

3.1.2 Contraindications

Transvenous endocardial pacing leads are contraindicated in the presence of severe tricuspid valvular disease and in patients with mechanical heart valves. The Solia S lead is additionally contraindicated for patients who cannot tolerate a single systemic dose of up to 1.0 mg of dexamethasone acetate (DXA).

3.1.3 Inclusion Criteria

All of the following inclusion criteria have to be fulfilled at the time of patient enrollment for study participation:

- Patient is a candidate for implantation of a BIOTRONIK pacemaker system, per standard guidelines. Single chamber, dual chamber, and CRT-P systems are allowed.
- Patient has an implant planned to utilize LBB area pacing within 30 days of consent
- Patient is able to understand the nature of the study and provide written informed consent
- Patient is available for follow-up visits on a regular basis for the expected duration of follow-up
- Patient accepts Home Monitoring® concept
- Patient age is greater than or equal to 18 years at time of consent

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

3.1.4 Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment include the following:

- Patient meets a standard contraindication for pacemaker system implant
- Patient is currently implanted with a pacemaker or ICD device
- Patient has had a previous unsuccessful attempt to place a lead in the LBB area
- Patient has planned cardiac surgical procedures or interventional measures within 3 months after implant
- Patient is expected to receive a heart transplant within 12 months
- Patient life expectancy is less than 12 months
- Patient has the presence of another life-threatening, underlying illness separate from their cardiac disorder
- Patient reports pregnancy at the time of enrollment
- Patient is enrolled in any other investigational cardiac clinical study during the course of the study

3.2 Study Procedures and Visits

Subjects will be implanted with a BIOTRONIK pacemaker system within 30 days after consent. Following implant, BIOTRONIK Home Monitoring® should be activated for all study subjects and the subject should be enrolled on the BIOTRONIK Home Monitoring Service Center website. Home Monitoring® data may be utilized to obtain required device treatment and performance data, as well as for evaluation of device collected information, such as pacing thresholds, sensing and impedance throughout the duration of the study. Additionally, Home Monitoring® data may be utilized by study site personnel to assist in the triage and diagnosis of system related adverse events between scheduled follow-ups. Therefore, it is important to confirm that Home Monitoring® is ON and transmitting data as soon as possible.

Required study visits and visit windows are described in Table 3. If a subject is eligible, consent is signed at the Enrollment Visit. All follow-up visit dates are calculated from the implant date of the initial BIOTRONIK pacemaker system. A visit assessment schedule is provided in Table 4.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Table 3: Visit Schedule

Visit Type	Window
Enrollment (consent)	N/A
Implant	≤30 days from consent
3 months post-implant	-14 days / +30 days
6 months post-implant	± 30 days
12 months post-implant	± 30 days

Table 4: Visit Assessment Schedule

Procedures	Enrollment Visit	Implant	3-Month Follow-up (-14/+30 days)	6-Month Follow-up (±30 days)	12-Month Follow-up (±30 days)
Informed consent	X				
Verification of inclusion and exclusion criteria	X				
Quality of Life (QOL) Questionnaire	X		X	X	X
12-lead ECG from pre-implant procedure and post-implant procedure. ECG characteristics pre- and post-LBB implant attempt.		X			
Investigator assessment of successful LBB lead implant		X			
Implanted system information		X			
Implantation information, including guide catheter, mapping system, selective vs. non-selective capture for the Solia S LBB lead, etc.		X			
Standard device evaluation, including Solia S LBB lead measurements and programming of device settings		X	X	X	X

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Procedures	Enrollment Visit	Implant	3-Month Follow-up (-14/+30 days)	6-Month Follow-up (±30 days)	12-Month Follow-up (±30 days)
Retrospective collection of demographics, medical history, cardiovascular medication*		X			
12-lead paced ECG and selective vs. non-selective capture for the Solia S LBB lead**			X	X	X
Adverse event reporting		X	X	X	X
Completion of eCRFs	X	X	X	X	X

*Baseline medical history is collected for all study subjects with an attempted implant procedure.
**All 12-lead paced ECGs performed per standard of care during study participation should be collected. One 12-lead paced ECG is required within the 3-month follow-up visit window through the 6-month follow-up visit window. If not available per standard of care, a 12-lead paced ECG should be performed at either the 3- or 6-month follow-up visit.

3.2.1 Pre-Screening

Prior to consent, the patient's medical history must be reviewed in order to ensure that the patient is an appropriate candidate for the study. This review includes verification of any available historical inclusion and exclusion criteria and confirmation of a plan to complete the implant within 30 days of consent. As part of the clinical study, informed consent must be obtained from the patient prior to initiating any study-related procedures.

3.2.2 Enrollment Visit

If the potential subject meets all inclusion and exclusion criteria as determined by pre-screening, the potential subject is informed about the study and asked to review and sign an Informed Consent Form. The potential subject should be provided with sufficient time to consider participation in the trial. The consent process, including discussion of the study, should be documented within the subject's medical record. A subject is considered provisionally enrolled in the study upon signing the Informed Consent Form. Consented subjects must be entered in the subject identification log and will be reflected on the electronic enrollment log once entered in the electronic data capture (EDC) system.

The following data collection, subject assessments, and reporting procedures are performed at the Enrollment Visit:

1. Verify that subject meets all of the inclusion criteria and none of the exclusion criteria at the time of patient consent

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

2. Obtain informed consent and upload the unredacted signed informed consent form to the Informed Consent eCRF[1]
3. Collect subject initials and date of birth
4. After informed consent has been obtained, subject completes the 36-Item Short Form Survey (SF-36) QOL questionnaire (see section 3.3.1)
5. Complete all required eCRFs and upload source documentation

3.2.3 Implant

Implant of a pulse generator system consisting of (1) any BIOTRONIK legally marketed pacemaker system, (2) BIOTRONIK Solia S 53 or 60cm pacing lead placed in the left bundle branch area, and (3) any legally marketed atrial and/or left ventricular pacing lead(s) depending on the individual study subject's device indication. Non-commercially available devices are excluded. To minimize potential risks, placement of the Solia S lead in the LBB area should be attempted no more than five times. A lead placement attempt in the LBB area is defined as extension of the helix of the Solia S lead into the subject's ventricular septum in the LBB area.

Implant should occur within 30 days of consent. If a subject is consented and more than 30 days elapse prior to an implant procedure, the subject must be re-consented within 30 days prior to implant to determine the subject's continued desire for participation and to re-confirm eligibility status. Following re-consent, the subject must complete an additional quality of life questionnaire, as measured by SF-36 (see section 3.3.1). For those subjects not re-consented within 30 days prior to implant, a Protocol Noncompliance eCRF will be required.

The following implant data and procedures will be collected for all subjects with a successful implant of the Solia S lead in the LBB area as defined in Section 2.1.1:

1. Collect and record 12-lead ECG from pre- and post-implant procedure. Document ECG characteristics such as native QRS duration pre-LBB implant attempt and paced QRS duration post-LBB implant from 12-lead ECG.
2. Obtain and document investigator assessment of protocol-defined successful LBB lead implant (refer to Section 2.1.1), which may include supportive documentation such as additional ECG recordings or EP mapping system recordings during implant procedure showing transitions and measurements
3. Collect and record implant information, including date, Solia S lead implant success in LBB area, number of LBB area placement attempts, pulse generator implant site, implant tools used for LBB area placement, implant time, mapping system, fluoroscopy usage and whether selective or non-selective LBB area pacing was achieved
4. Collect implanted system information, including manufacturer, model, and serial number for the pulse generator and each implanted BIOTRONIK pacing

[1] Sites that are unable to upload signed informed consents will be asked to provide a copy of the IRB and/or institutional policy stating they are not allowed to upload unredacted source documentation.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

lead. Additionally, collect manufacturer for each implanted non-BIOTRONIK pacing lead. Collect which lead is connected to each pulse generator port.

5. Perform standard post-implant device interrogation
   - Confirm device programming and settings, including activation of the recommended device programming (see Table 5)
   - Collect and record Solia S LBB lead measurements, including pacing threshold, R-wave sensing, and pacing impedance using post-implant device interrogation with programmer
   - Verify device is pacing and sensing appropriately
   - Obtain programmer PDF or printout of device interrogation, including final device settings and measurements
6. Review for any reportable adverse events, device deficiencies or complaints
7. Retrospective collection of pre-procedure information from the medical record, including demographics, medical history, and cardiac medications
8. Complete all required eCRFs and upload source documentation

3.2.4 Device Programming

Postoperative bradyarrhythmia settings including pacing voltages and base rate are at the discretion of the investigator. At the end of the implant procedure, these general programming guidelines are recommended:

Table 5: Recommended Programmed Parameters

Parameters	Programmed Setting
BIOTRONIK Home Monitoring®	ON
LBB Lead capture control	ON or ATM

BIOTRONIK Home Monitoring® should be activated to allow collection and evaluation of daily remote data and to support remote follow-up visits. Study subjects should be registered in the BIOTRONIK Home Monitoring Service Center as soon as possible following implant.

To ensure Home Monitoring data is available as soon as possible after implant, please confirm:

- The subject has been given a CardioMessenger®, or confirmed that a CardioMessenger® will be shipped to the subject
- The subject's residence has cell coverage for data transmission
- The subject understands the need to plug in the CardioMessenger® at home for the device to transmit data

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

3.2.5 Solia S Unsuccessful Implant Attempt

If the Solia S implant in the LBB area is unsuccessful, the subject will be considered an unsuccessful implant attempt and will be followed in a 30-day safety registry prior to being exited from the study. An implant attempt in the LBB area is defined as the Solia S lead coming into contact with subject's ventricular septum with the intent to place the Solia S lead in the LBB area.

The following implant data and procedures will be collected for all subjects with an unsuccessful implant attempt of the Solia S lead in the LBB area:

1. Collect and record implant information, including date, the reason for the attempt being unsuccessful, and the final Solia S lead tip location (if successfully implanted in a location other than LBB area)
2. Collect and record the model and serial number of the attempted Solia S lead
3. Collect implanted system information, if applicable, including manufacturer, model, and serial number for the pulse generator and each implanted BIOTRONIK pacing lead. Additionally, collect manufacturer for each implanted non-BIOTRONIK pacing lead. Collect which lead is connected to each pulse generator port.
4. Collect implant information, if applicable, including the number of LBB area placement attempts, pulse generator implant site, implant tools used for LBB area placement, implant time, mapping system (if used), and fluoroscopy usage.
5. If lead tested in LBB area, obtain and document investigator assessment of protocol-defined success criteria (refer to Section 2.1.1), which may include supportive documentation such as ECG recordings or EP mapping system recordings from implant procedure showing transitions and measurements
6. Review for any reportable adverse events, device deficiencies or complaints
7. Retrospective collection of pre-procedure information from the medical record, including demographics, medical history, and cardiac medications
8. Complete all required eCRFs and upload source documentation

3.2.6 3-Month, 6-Month, and 12-Month Follow-up Visits

Three (3) months (- 14 days, + 30 days), six (6) months (± 30 days) and twelve (12) months (± 30 days) after implantation, subjects will undergo an assessment of their implanted system. It is encouraged to perform the 3-Month Follow-up Visit in-office. However, all follow-up visits may be performed in-office or remotely, per the site's standard of care. Visits completed outside of the target window will require completion of a Protocol Noncompliance eCRF; however, this is preferred to a missed visit.

1. To minimize bias, SF-36 administration should be performed prior to routine device interrogation or other study procedures occurring on the same day as the SF-36 completion: Subject completes SF-36 (see Section 3.3)

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Additionally, the following data must be collected at the 3-month, 6-month, and 12-month follow-ups:

2. Obtain device-based measurements
   - Determine Solia S LBB lead impedance
   - Determine Solia S LBB lead R-wave sensing amplitude
   - Determine Solia S LBB lead pacing threshold at 0.4 ms pulse width
   - Collect a 12-lead paced ECG and determination of selective vs. non-selective capture of LBB area (if assessed). All 12-lead paced ECGs performed per standard of care during study participation should be collected. One 12-lead paced ECG is required within the 3-month follow-up visit window through the 6-month follow-up visit window. If not available per standard of care, a 12-lead paced ECG should be performed at either the 3- or 6-month follow-up visit.
3. Collect final device programming and settings and confirm activation of the recommended device programming (see Section 3.2.4)
4. Obtain documentation of initial device settings, final device settings, measurements, and diagnostics:
   - Programmer PDF or printout of device interrogation, or
   - BIOTRONIK Home Monitoring® CardioReport
5. Review for any new reportable adverse events, device deficiencies or complaints or updates to previously reported events. This includes an interview with the subject by delegated site personnel, either via phone call or an in-person conversation, along with medical record review. The interview to assess AEs must occur within 7 days (± 7 days) of the CardioReport "Last message" date or device interrogation.
6. Complete all required eCRFs and upload source documentation

3.2.7 System Revision

A system revision eCRF is required any time any of the implanted system components are revised such as pocket revision, lead repositioning, lead surgically abandoned, lead explant/extraction/removal, lead replacement. If during the system revision the Solia S lead implanted in the LBB area is explanted, the subject will be exited from the study. All explanted devices should be returned to the manufacturer for analysis.

The following data and procedures are collected for system revisions:

1. Prior to revision procedure, perform a device interrogation:
   - Evaluate device diagnostics, electrical parameters, and programmed parameters to ensure the device was correctly pacing and sensing
   - Obtain pre-revision programmer PDF or printout of device interrogation, including final device settings, measurements, and device diagnostics

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

2. Collect implant information for revised or explanted system components
   - Date of revision procedure
   - Reason for revision procedure
3. Collect implanted system information for new components, including manufacturer, model, and serial number for BIOTRONIK components and manufacturer for non-BIOTRONIK components. Collect which lead is connected to each pulse generator port in the case of any changes.
4. Following revision procedure, perform a device interrogation:
   - Collect device programming and settings at end of revision procedure and confirm the activation of the recommended device programming (see Section 3.2.4)
   - Evaluate device diagnostics, electrical parameters, and programmed parameters to ensure the device is correctly pacing and sensing
   - Determine Solia S LBB lead impedance
   - Determine Solia S LBB lead R-wave sensing amplitudes
   - Determine Solia S LBB pacing threshold at 0.4 ms pulse width at the end of intervention
   - Obtain post-revision programmer PDF or printout of device interrogation, including final device settings, measurements, and device diagnostics
5. Review for any new reportable adverse events and updates to previously reported adverse events
6. Complete all required eCRFs and upload source documentation
7. Document any reportable adverse event, device deficiencies or complaints during the procedure by using the respective eCRF

3.3 Study Assessments

3.3.1 Quality of Life Questionnaire Administration

This clinical protocol makes use of the 36-Item Short Form Health Survey (SF-36v1) questionnaire (RAND 2022) to collect data about the effect of LBBAP on patient-reported quality of life (QOL). The SF-36 survey will be completed at the Enrollment Visit and all follow-up visits. The survey may be administered via telephone for follow-up visits. The SF-36 survey consists of eight different scales measuring a patient's physical and mental health. The four scales that incorporate the patient's overall physical health status include physical functioning, role-physical, bodily pain, and general health. The four scales that incorporate the patient's overall mental health include vitality, social functioning, role-emotional, and mental health.

It is important that the administrator follow a standard process, as follows. The goal is to minimize the influence on the subject by limiting their interaction and verbal exchanges while the subject assessment is being completed. It is important that the

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

subject, and not their spouses or other individuals, are providing responses to the questionnaire questions. Ample, uninterrupted time should be provided for the subject to complete the questionnaire.

All subjects should be encouraged to answer each question. If the subject asks for clarification of a particular item, read the question to the subject verbatim. If the subject still asks for clarification, explain to them that they should use their own interpretation of the question.

Once a questionnaire is completed, check to make sure each question has been answered and that there is only one answer clearly marked for each question. If a subject elects not to answer a specific question(s), it is preferred this is indicated on the questionnaire.

Corrections in the case of multiple responses should be made with a single line-through which is initialed and dated by the person completing the form (i.e. site personnel for a telephone visit or the subject for an in-office visit).

Questionnaires in a language understandable to the subject should be used. Sites should contact BIOTRONIK to request questionnaires in additional languages.

The questionnaire is located in Appendix B: SF-36.

3.4 Study Exits

Once a subject is enrolled and successfully implanted, every effort should be made to continue to follow the subject in the clinical investigation. However, it is possible that some subjects will decline to participate further, change geographic location, or become non-compliant with the visit schedule. Other possible reasons for study exits prior to termination of the study are noted below.

Upon study exit, the subject's medical records should be reviewed to ensure that all protocol defined adverse events, device deficiencies or complaints have been documented in the EDC system. All previously unreported, protocol defined adverse events should be documented on Adverse Event eCRFs. A Study Exit eCRF must be completed to document the study exit date and reason. Appropriate source documentation must be uploaded to the Study Exit eCRF. For all subjects that are enrolled, data collected through the date of exit may be used for analysis.

3.4.1 Screen Failure

If a Solia S implant was planned but not performed or the investigator decided after depiction of the subject's cardiac conduction system that the Solia S lead is not suitable for placement in the LBB area and the Solia S was not attempted to be implanted in the LBB area, the subject is exited. The reason for study exit must be provided. The date of study exit is determined by the site (e.g. date determined would not go forward with an implant of Solia or date of implant procedure where it was determined LBB area was not suitable).

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

3.4.2 Unsuccessful Implant

If a Solia S lead was attempted to be implanted in the LBB area, but the attempt was unsuccessful, the subject will be followed in a 30-day safety registry. On or after 30 days post-implant (+ 30 days), the site should conduct a remote visit (e.g. telephone interview) with the subject to collect any adverse events occurring since implant. Additionally, the site should review the subject's medical records for any unreported adverse events. Any adverse events should be reported on an Adverse Event eCRF. After the visit is completed, a Study Exit eCRF should be completed. The date of study exit is the date of the safety registry 30-day follow-up visit.

3.4.3 Subject Withdrawal of Consent

Subjects may withdraw their consent for study participation at any time during their study participation without stating the reason for withdrawal and without any unfavorable consequences. All data collected until the date of withdrawal will be used for analysis. A Study Exit eCRF will be completed by the clinical site including the reason(s) for subject withdrawal of consent if available. The date of study exit is the date of withdrawal of consent.

3.4.4 Subject Moved from Investigational Center

Subjects that have moved and cannot return to the investigational center for follow-up visits may be exited. Prior to exiting, the study site should attempt to identify where the subject is relocating and work with BIOTRONIK to determine if transfer of care to another investigational center is possible. In the event transfer to another center is not possible, the exit reason should be selected as "Subject has moved from investigational center" and the date of subject acknowledgement of move should be reported as date of exit.

3.4.5 Investigator-Initiated Withdrawal

In addition to subject initiated withdrawal of consent, a study site investigator may determine that a subject should be withdrawn for other reasons such as following with a different physician, noncompliance, etc. Details related to investigator-initiated withdrawal such as reason for withdrawal and attempts made to retain subject should be collected. The exit reason should be selected as "Investigator initiated withdrawal". The investigator determined end date of subject participation should be reported as the date of exit.

3.4.6 Subject Death

In the event of subject death during study participation, personnel at the study site are requested to notify BIOTRONIK promptly by completing an Adverse Event eCRF (if applicable) and a Study Exit eCRF. All actions taken, which were initiated to gain further information must be documented in writing and provided to BIOTRONIK.

The date of study exit is the date of death.

The following information will be required for any subject death:

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

- Death certificate, death report signed by the investigator, or relevant medical records that include:
  - Date of death
  - Primary cause of death
  - Any other circumstances surrounding the death
  - Investigator's assessment of relatedness to study device, study system, or procedure
  - COVID 19 status, if available
  - Solia S lead return status, if available

Whenever possible, devices that are explanted must be returned to BIOTRONIK for analysis.

3.4.7 Solia S LBB Lead Extraction

Any subject who has the Solia S LBB lead explanted will be withdrawn from the clinical investigation. After documentation of the system revision procedure (see Section 3.2.7), a Study Exit eCRF should be completed. The date of study exit is the date that the Solia S LBB lead is explanted.

Whenever possible, devices that are explanted must be returned to BIOTRONIK, Inc. for analysis.

3.4.8 Lost to Follow-up

Subjects lost to follow-up are those with whom contact is lost despite the investigator's best efforts to locate the subject and for whom Home Monitoring® data is no longer available to the study site or Home Monitoring® has been deactivated. Study sites should attempt to contact these subjects in order to maintain study visit compliance and all contact attempts should be documented. At a minimum, the site should make two attempts to contact the subject by phone and one attempt by certified mail.

In the event the subject cannot be contacted using the above methods, the subject is exited from the clinical investigation by completing a Study Exit eCRF.

The date of exit is the later of the date of last documented successful contact with the subject or date of last entered visit should be reported as the date of exit.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

4 Statistical Design and Analysis Plan

4.1 Analysis of Study Endpoints

4.1.1 Primary Endpoint 1 - Serious Adverse Device Effect (SADE)-Free rate through 3 Months Post-implant

The purpose of primary endpoint 1 is to evaluate the serious lead related adverse device effects related to Solia S lead utilized or attempted to be implanted in the LBB area and serious implant procedure events related to the Solia S LBB lead that occur through 3 months post-implant.

The following hypotheses have been defined to evaluate the primary endpoint "Serious adverse device effect (SADE)-free rate through 3 months post-implant":

H_0: The serious adverse device effect (SADE)-free rate through 3 months post-implant is less than or equal to 87.5%

SADE-free rate ≤ 87.5%

H_a: The serious adverse device effect (SADE)-free rate through 3 months post-implant is greater than 87.5%

SADE-free rate > 87.5%

Primary endpoint 1 will be evaluated by performing an exact, binomial test comparing the observed proportion (overall SADE-free rate through 3 months) to the performance goal of 87.5%. The lower, two-sided 95% confidence bound for the overall SADE-free rate must be greater than 87.5% to reject the null hypothesis (H_0), which would demonstrate evidence that the SADE-free rate is significantly higher than 87.5%.

4.1.2 Primary Endpoint 2 – Implant Success

The purpose of primary endpoint 2 is to evaluate the implant success rate of Solia S lead in the LBB area. Implant success is defined in Section 2.1.1.

The following hypotheses have been defined to evaluate the primary efficacy endpoint:

H_0: The implant success rate of Solia S lead in the LBB area is less than or equal to 80%.

Implant Success Rate ≤ 80%

H_a: The implant success rate of Solia S lead in the LBB area is greater than 80%.

Implant Success Rate > 80%

Primary endpoint 2 will be evaluated by performing an exact, binomial test comparing the observed proportion (implant success rate) to the performance goal of 80%. The lower, two-sided 95% confidence bound for the overall implant success rate must be greater than 80% to reject the null hypothesis (H_0), which would demonstrate

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

evidence that the rate of successful Solia S LBBAP implants is significantly higher than 80.0%.

4.1.3 Secondary Endpoints

4.1.3.1 Secondary Endpoint 1: Quality of Life (QOL) through 12 Months Post-implant

The purpose of secondary endpoint 1 is to evaluate the improvement in QOL for patients with successful Solia S lead implantation in the LBB area. Specifically, the physical function scale of the SF-36 will be used as it has been shown to be the best all-around measure of physical health (Ware JE Jr. et al. 2000). The QOL scale is standardized such that a higher score indicates better physical health.

The following hypotheses have been defined to evaluate the improvement in quality of life:

H_0: The improvement in quality of life through 12 months post-implant for subjects with successful Solia S lead implanted in the LBB area is less than or equal to 2.8

$$\text{Improvement in QOL}_{\text{Physical Function Scale}} \leq 2.8$$

H_a: The improvement in quality of life through 12 months post-implant for subjects with successful Solia S lead implanted in the LBB area is greater than 2.8

$$\text{Improvement in QOL}_{\text{Physical Function Scale}} > 2.8$$

Secondary endpoint 1 will be evaluated by performing an exact one-sample t-test comparing the mean improvement in QOL from baseline to 12 months post-implant to the performance goal of 2.8. The lower, two-sided 95% confidence bound for the improvement in QOL must be greater than 2.8 to reject the null hypothesis (H_0), which would demonstrate evidence that the improvement in QOL is significantly higher than 2.8.

4.1.3.2 Other Secondary Endpoints

Descriptive analysis will be completed for the other secondary endpoints.

4.2 Sample Size Estimation

The investigation is designed to limit the number of subjects involved while still exposing the device implanted per an investigational indication to a sufficiently large population in order to ensure a representative and statistically meaningful sample.

4.2.1 Assumptions for Primary Endpoint 1 - Serious Adverse Device Effect (SADE)-Free Rate through 3 Months Post-Implant

Prior studies evaluating the safety of Solia S when implanted in the right ventricle has demonstrated a high SADE-free rate, between 94.3% and 98.5% (Master Study of the Siello Pacemaker Lead and Siello IDE Clinical Study, data on file). When implanting in the LBB area, the expected safety needs to consider the change in

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

implant location. A summary of published data that includes safety information for leads implanted in the LBB area is presented in Table 6.

Table 6: LBB Area Pacing—Published Safety Results

Study	Mean Follow-up Duration (months)	Total Implanted Subjects (n)	Subjects without SADE (n)	SADE-Free Rate	95% CI – Lower Bound
Su L et al. 2021	18.6	618	600	97.1%	95.4%
Vijayaraman P et al. 2019	5.2	93	87	93.6%	86.4%
De Pooter J et al. 2020	3.0	44	39	88.6%	75.6%
Li X et al. 2019	3.0	30	29	96.6%	81.9%

Based on this information, it is anticipated the Solia S lead will have a safety profile similar to published literature for leads implanted in the LBB area with an expected SADE-free rate of at least 93.0%. The assumed performance (93%) and performance goal of 87.5% are compared to the published safety results in Figure 3.

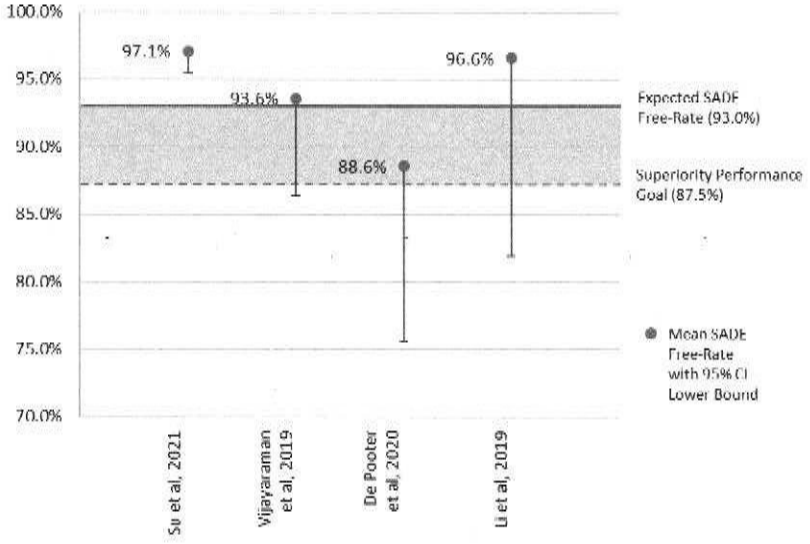

Figure 3: Assumed Safety Performance Compared to Published Results

The estimated sample size required to evaluate primary endpoint 1 is based on a superiority comparison of overall Solia S lead serious adverse device effect free-rate to 87.5% through 3 months post-implant. The sample size for primary endpoint 1 was calculated based on the following assumptions.

Assumptions:

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

- Study Design: Non-randomized
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Performance Goal for SADE-Free Rate through 3 months post-implant: 87.5%
- Expected SADE-Free Rate through 3 months post-implant: 93% (Based on Literature Review/Master Study)
- Test basis: Exact binomial test
- Attrition Rate: 5%

For primary safety endpoint 1, a total of 247 evaluable Solia S leads would be required to demonstrate superiority to a SADE-free rate of 87.5%. Assuming a 5% attrition rate, a total of 260 (= 247 / 0.95) patients with a Solia S lead would be required to be enrolled to evaluate Primary Safety Endpoint 1.

4.2.2 Assumptions for Primary Endpoint 2 – Implant Success

Expectations for implant success are based on published findings for LBB area pacing (Table 7).

Table 7: LBB Area Pacing—Published Implant Success Results

Study	Total Subjects (n)	Subjects with successful implant (n)	Success Rate	95% CI – Lower Bound
Su L et al. 2021	632	618	97.8%	96.3%
Padala S et al. 2020	341	305	89.4%	85.7%
Li X et al. 2021	246	235	95.5%	92.1%
Vijayaraman P et al. 2019	100	93	93.0%	86.0%
Wang J et al. 2020	66	61	92.4%	83.1%
De Pooter J et al. 2020	50	44	88.0%	75.8%
Li X et al. 2019	33	30	90.9%	75.7%
Zhang S et al. 2021	33	29	87.9%	72.1%
Huang W et al. 2020	63	61	96.8%	88.5%

It is expected that the Solia S when implanted in the LBB area will have an implant success of 88.0%, which is similar to published rates. The assumed performance (88.0%) and performance goal of 80.0% are compared to the published safety results in Figure 4.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

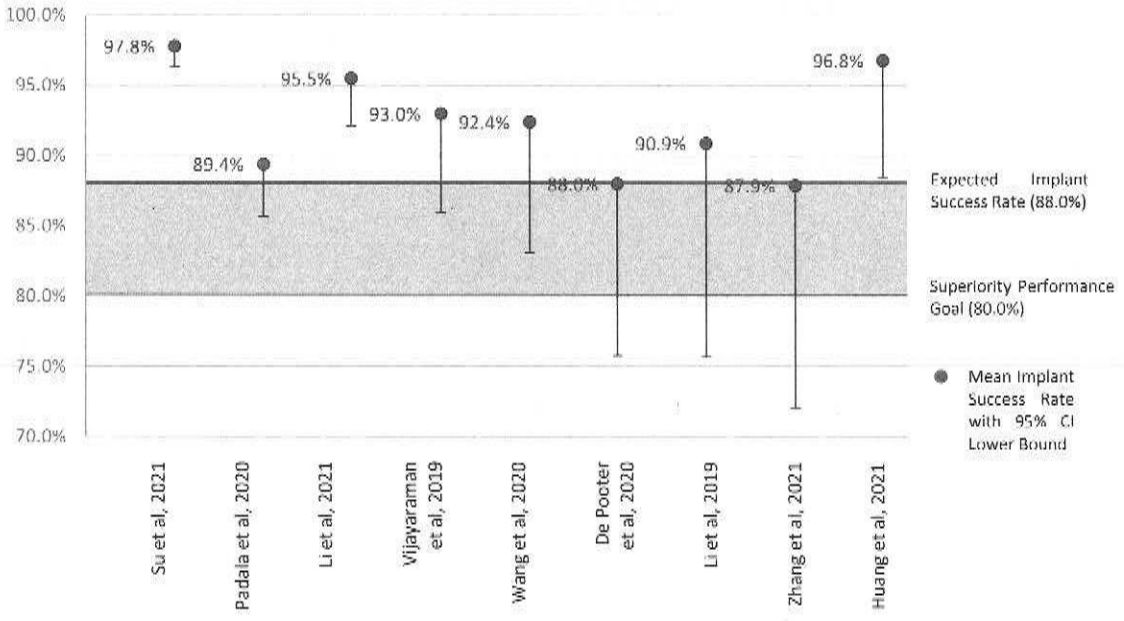

Figure 4: Assumed Implant Success Compared to Published Results

The estimated sample size required to evaluate primary endpoint 2 is based on a superiority comparison of overall Solia S leads successfully implanted to 80%. The sample size for primary endpoint 2 was calculated based on the following assumptions.

Assumptions:

- Study Design: Non-randomized
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Performance Goal for Successful Implant Rate: 80%
- Expected Successful Implant Rate: 88%
- Test basis: Exact binomial test
- Attrition Rate: 5%

For primary endpoint 2, a total of 175 evaluable Solia S leads would be required to demonstrate superiority to a successful implant rate of 80%. Assuming a 5% attrition rate, a total of 184 (= 175 / 0.95) patients with a Solia S lead would be required to be enrolled to evaluate primary endpoint 2.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

4.2.3 Assumptions for Secondary Endpoint 1 – Quality of Life (QOL)

Prior studies evaluating the quality of life in elderly patients receiving dual-chamber pacemakers with standard RV pacing have demonstrated modest improvement (ranging from 2.7 to 4; weighted mean of 2.8) in QOL as assessed by the SF-36 physical function scale from baseline (pre-implant) to 12 months post-implant (Fleischmann KE et al. 2006, Yu CM et al. 2014). More recently, Li H et al. (2021), found patients experiencing pacemaker-induced cardiomyopathy that were upgraded from RV pacing to LBB area pacing had a higher score in the physical function scale by 18.2 points at 12 months post-upgrade. At 24 months post-implant, in a crossover study, Kronborg MB et al. 2014 showed a 5-point improvement as measured by the physical function scale comparing His or para-His pacing to RV pacing. However, this improvement was not shown to be statistically significant. Other studies on conduction system pacing have noted improved QOL in patients receiving this therapy (Lustgarten DL et al. 2015, Occhetta E et al. 2006).

Based on this information, it is anticipated that patients with successful LBB area pacing with the Solia S lead will have an improvement in QOL, as measured by the SF-36 Physical Function score, of at least 10 from pre-implant baseline to 12 months post implant. This improvement in the Physical Function Score with LBB area pacing using a Solia S lead is the expected improvement due to receiving a pacemaker system (pre-implant baseline to RV pacing, average improvement in QOL score = 2.8) plus the additional expected benefit due to utilizing LBB area pacing as compared to RV pacing (expected improvement in QOL score = 7.8; combining LBB vs RVp from Li H et al. and Kronborg MB et al, weighted mean = 7.8). For the sample size calculation, an expected improvement in the Physical function Score was rounded to 10.

The estimated sample size required to evaluate secondary endpoint 1 is based on a superiority comparison of the improvement in QOL (physical function scale) to the expected improvement with RV pacing of 2.8 points. The sample size for secondary endpoint 1 was calculated based on the following assumptions.

Assumptions:

- Study Design: Non-randomized
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Standard deviation: 30
- Performance Goal for $QOL_{\text{Physical Function Scale}}$ Improvement: 2.8
- Expected $QOL_{\text{Physical Function Scale}}$ Improvement: 10
- Test basis: Exact one-sample t-test

For secondary endpoint 1, 139 evaluable QOL paired baseline and 12-month measurements would be required to demonstrate superiority to an improved QOL of 2.8 based on a standard deviation of 30. The assumed standard deviation for SF-36 Physical Function Scale score is based on findings from multiple sources using SF-36

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

for RV pacing. (Kronborg MB et al. 2014, Li H et al. 2021, Link MS et al., 2004, Yu CM et al. 2014)

4.2.4 Sample Size Summary

The required sample sizes for the primary endpoints and secondary endpoint 1 are summarized in Section 4.2. The primary safety endpoint is driving the overall study sample size. Assuming a 5% attrition rate, a total sample size of 260 subjects has been estimated.

BIOTRONIK plans to pool data from other prospective data sources to supplement the LBB area pacing population; thus, the number of prospectively enrolled subjects in this study may be less than 260.

4.2.5 Replacement of Subjects

To ensure sufficient primary endpoint evaluable data, enrolled subjects with a successful LBB area implant who exit the study prior to the 3-month primary endpoint follow-up due to death, lost-to-follow up, investigator initiated withdrawal, subject moved from investigational center, or withdrawal of consent may be replaced as long as enrollment is ongoing and subject did not experience a primary endpoint event. These subjects do not count towards the overall planned prospectively-enrolled subject number of 260.

4.2.6 Maximum Number of Subjects per Site

Enrollment at a single site will be limited to no more than 20% of the projected 260 subject total prospective study enrollment (approximately 52 subjects).

4.3 Data Analysis Plan

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions and cross tabulations will be presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

4.3.1 Analysis Population Definitions

Table 8: Study Analysis Populations

Analysis Population	Definition
Intent-to-Treat (ITT) – Primary Safety Endpoint	This ITT population is defined as • all enrolled subjects (subjects with successfully implanted Solia S in the LBB area) and • subjects with an unsuccessful implant attempt of the Solia S in the LBB area who had a qualifying primary safety endpoint event prior to their exit from the study.
Intent-to-Treat (ITT) – Primary Efficacy Endpoint	This ITT population is defined as • all enrolled subjects (subjects with successfully implanted Solia S in the LBB area) and • subjects with an unsuccessful implant attempt of the Solia S in the LBB area.

4.3.2 Analysis Methods

All clinical data will be analyzed based upon the pre-defined analysis populations. The following methods will be used to evaluate the study endpoints.

Both primary endpoints will be evaluated in the ITT populations. For the primary safety endpoint, a Kaplan-Meier survival analysis (time-to-event) will be performed and subjects who have sufficient follow-up data (at least 76 days of follow-up) or experienced the primary safety endpoint will be included in the primary safety endpoint analysis. Exact one-sided Binomial Proportion test will be used to evaluate primary endpoint 1 and primary endpoint 2 against the hypothesis. For the evaluation of primary endpoint 1, subjects without a primary safety endpoint event who drop out prior to the 3-month follow-up will be excluded to avoid overestimation of the SADE-free rate.

Analyses of the secondary endpoints will be carried out on the ITT analysis populations.

For a successful study, both primary endpoints must be met to control the type I error at the 1-sided 0.025 level. Secondary endpoint 1 will only be tested if both primary endpoints are successful.

4.3.3 Provision for Pivotal Analysis

A pivotal analysis and interim report of the primary endpoint data is planned after 3-month follow-up data is collected for the BIO-CONDUCT study patients and the minimum sample size for primary endpoint 1 and primary endpoint 2 has been met. Further interim analyses are not planned and there are no statistical criteria to stop the study early. Thus, no adjustment of the significance level is planned due to the pivotal analysis.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Data collection will continue until 12-month follow-up data is collected. Analysis of secondary endpoint 1 will be included in the final report.

4.3.4 Handling of Missing or Unused Data

All reasonable methods will be taken to ensure a minimum of missing data, including site monitoring, training, and corrective actions, if required, ongoing review of collected data for accuracy and completeness, and repeated, documented attempts to contact subjects with missing study visits. Any reasons for missing data or withdrawal from the study will be documented when possible. The impact of missing data on conclusions about the primary study endpoint will be examined in sensitivity analyses, which may include multiple imputation methods, if warranted.

Missing QOL data at either the baseline or 12-month follow-up visit affects the number of subjects that can be included in the secondary endpoint QOL analysis. It is anticipated that subjects may either forget or choose not to answer one or more of the questions in the QOL. In some cases, subjects may also provide two answers for one or more of the questions. There is no appropriate method to correct these QOL questionnaires after the subject completes the visit.

If needed to ensure sufficient subjects to analyze secondary endpoint 1, an analysis using the last observation carried forward principle and/or average replacement for missing QOL answers or QOL questions with multiple answers may be performed. Additionally, last observation carried forward may be used in cases for which the QOL questionnaire is not completed at the 12-month visit. If there are more than 10% of subjects with missing answers, an assessment of the cause for the missing answers will be performed. If the assessment is such that a random cause can be assumed, then a multiple imputation technique that accounts for variability in imputation will be utilized. Additionally, where missing data are imputed, sensitivity analyses will be completed.

4.3.5 Subgroup Analysis

Secondary analyses of primary and secondary endpoints evaluating subjects ≥65 years of age will be conducted. There is no formal hypothesis for this subgroup analysis.

4.3.6 Poolability Analysis

The distribution in SADE-free rates across centers will be examined. The significance of differences in rates between centers will be initially tested using a Kruskal-Wallis test statistic, with an associated p-value of 0.15 or less considered evidence of center differences. In addition, a Cochran-Mantel-Haenszel test with continuity adjustment will be used to assess the poolability across centers. If evidence is found of center differences, then the reasons for the differences will be explored using Cox and logistic regression methods to determine if any baseline subject risk factors are explanatory.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

4.3.7 Sex, Race, and Region Analyses

Any differences between sexes or race in study results will be analyzed and reported but there are no pre-specified tests of the statistical significance for differences. Comparisons of results between clinical site regions (U.S vs. Outside of U.S) will also be conducted.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

5 Adverse Events

In the course of the study, undesired medical events may occur in participating subjects, which are called adverse events (AEs). Furthermore, device deficiencies (DD) or complaints may also be observed. All protocol-defined AEs and DDs shall be documented and reported to BIOTRONIK using the respective electronic case report forms (eCRFs) provided within the EDC system.

5.1 General Definitions

5.1.1 Adverse Event (AE)

An AE is defined as an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device and whether anticipated or unanticipated. This includes:

- Events related to the study device
- Events related to implanted system
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the use of study devices.

Source: ISO 14155:2020 3.2

5.1.2 Adverse Device Effect (ADE)

An ADE is an AE related to the use of a study device. This includes:

- AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the study device.
- Any event resulting from use error or from intentional misuse of the study device.

Source: ISO 14155:2020 3.1

5.1.3 Unanticipated Adverse Device Effect (UADE)

A UADE is 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.

It is important to note that random component failures or problems caused by misuse of the product are not considered unanticipated adverse device effects.

Additionally, events that are unexpected are not necessarily unanticipated (e.g. a lead dislodgement is unexpected but is identified as a potential risk in the device

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Technical Manual and would therefore be an anticipated AE.) The final determination of an event being classified as an unanticipated event will be determined by BIOTRONIK.

If a UADE occurs, then the investigator is required to notify BIOTRONIK and the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the effect in accordance with FDA regulations. Devices that are returned due to suspected relation to an adverse event will be sent to BIOTRONIK SE & Co. KG in Berlin, Germany, for analysis. Details of reporting requirements and timelines for Investigators and BIOTRONIK are described in Table 9 and Table 10, respectively.

Source: 21 CFR Part 812.3(s)

An Unanticipated Serious Adverse Device Effect (USADE) is an SADE which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

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

Source: ISO 14155:2020 3.51

5.1.4 Serious Adverse Event (SAE)

An SAE is an AE 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 one or more of the following:

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 or prolonged 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) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. Events for which subjects are hospitalized for less than 24 hours without change of date will not be documented as serious, unless one or more of the other seriousness criteria are fulfilled.

Source: ISO 14155:2020 3.45, plus 42 CFR Part 11.10

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

5.1.5 Serious Adverse Device Effect (SADE)

An SADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

Source: ISO 14155:2020 3.44

5.1.6 Device Deficiency (DD)

Device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. This includes

- Malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
- Device deficiencies related to the study device or the comparator.

Source: ISO 14155:2020 3.19

5.1.7 Definition of Device Complaint

A device complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

Source: 21 CFR Part 820.3(b)

5.2 Causality Assessment

The relationship between the use of the study device (including the surgical procedure and non-study devices or components) and the occurrence of each adverse event shall be assessed and categorized, considering the presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness, or risk factors.

Each adverse event will be classified according to four different levels of causality. The investigator will use the following definitions to assess the relationship of the adverse event to the study device or procedures and the sponsor or sponsor designee will review the investigator's categorization:

Not related: Relationship to the device or procedures can be excluded.

Possible: The relationship with the use of the study or non-study device 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 where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable: The relationship with the use of the study or non-study device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

Causal relationship: The serious adverse event is associated with the study or non-study device or with procedures beyond reasonable doubt.

The investigators will distinguish between the adverse events related to the study device, those related to the device procedures (any procedure specific to the study device), and those related to a non-study device or component. Procedure related events refer to the procedure related to the application of the study device only and therefore not to any other procedure for other devices and not to any other procedures or treatments applied later throughout the clinical study, except for a revision of the study device (e.g. Solia S LBB lead reposition post-implant).

An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use or application.

5.3 Protocol Defined Reportable Adverse Events

Study site investigators will be required to assess and report to BIOTRONIK, by completing the appropriate eCRF, the following types of events experienced by the subject after consent:

- All serious adverse events
- All adverse events with causal, probable, or possible relation to
  - study device
  - implanted system
  - procedures involved with implanting, using, or testing the study device
- Any adverse device effects, regardless of severity and including both previously reported and unanticipated adverse device effects

Additionally, any device deficiency or complaint needs to be reported.

Adverse events with onset after consent through the study exit date are collected for 1) enrolled subjects and 2) subjects with an unsuccessful implant attempt through 30 days in the safety registry (refer to Section 2.2). Additionally, if a subject is exited as a screen failure after having started the implant procedure (e.g. Solia S lead never comes in contact with the subject or it is determined prior to lead insertion that LBB placement is not appropriate for the subject), adverse events potentially related to the device or procedure will be collected.

Pre-existing conditions (underlying conditions present prior to obtaining subject consent) that are clearly documented in the subject's medical record are not reportable unless there is an increase in severity or frequency or a change from baseline during the course of the study.

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval

5.4 Reporting Adverse Events

5.4.1 Site Reporting

The study site should report each protocol defined, reportable adverse event to BIOTRONIK via completion of an Adverse Event eCRF. Adverse events should be reported as soon as information is available, even if this results in an incomplete eCRF. Study site investigators are required to follow-up on all ongoing reportable events as long as the subject participates in the study, until the study is terminated, or until the event has been resolved, whichever comes first.

The investigator will be required to assess and characterize each protocol defined adverse event's relatedness to the study device, procedure, and non-study device or component; seriousness, outcome, treatment or action taken.

Multiple adverse events may occur simultaneously. The study site investigator will be requested to identify the number of medically independent events and characterize each event with a single primary diagnosis. The primary diagnosis may describe an event consisting of several clinically recognizable features, symptoms, or secondary diagnoses. All observed symptoms and secondary diagnoses should be properly documented in the Adverse Event eCRF. In addition, all actions taken or treatments should also be reported within the Adverse Event eCRF.

The study site has the responsibility to ensure that all source documentation relevant to the adverse event is available, complete, final and signed, and provided to BIOTRONIK. This includes source documentation from other parties, such as family members, other treatment facilities, hospitals, etc. Copies of all supporting documents should be uploaded into the Adverse Event eCRF as soon as they are available. For potential endpoint events, these documents may also support CEC adjudication.

Study sites are required to adhere to applicable regulations and reviewing IRB reporting requirements for adverse events. Refer to Table 9 for further details on UADE reporting timing requirements. The adverse events that an IRB considers reportable are dependent on the particular IRB. A copy of the IRB adverse event notification should be provided to BIOTRONIK.

Additionally, study sites may report adverse events through MedWatch FDA's adverse event reporting tool for market released devices. As defined in BIOTRONIK's internal procedures, study adverse events may be reported by BIOTRONIK through manufacturer's MedWatch reports.

5.4.2 Sponsor Reporting

BIOTRONIK may determine that study adverse events meet the manufacturer's reporting requirements through MedWatch reports. Refer to Table 10 for further details on UADE reporting timing requirements.

5.4.3 Adverse Events for Primary Endpoint 1 Analysis

The purpose of primary endpoint 1 is to evaluate the overall incidence of serious Solia S LBB lead related adverse device effects and serious implant procedure events

CONFIDENTIAL: Do not copy or distribute without BIOTRONIK approval