Plexa Registry

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Study Protocol and
Statistical Analysis Plan
March 1, 2017

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Clinical Protocol for the Plexa Registry

March 1, 2017

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PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the Plexa Registry protocol and any attachments, 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 US federal regulations, ICH and GCP guidelines.

PRINCIPAL INVESTIGATOR:

Signed:

_____
Name (please print)

_____ _____
Signature Date

SUMMARY

Title:	Plexa Registry
Design:	Prospective, single-arm, non-randomized, multi-center registry
Purpose:	To confirm the long-term safety and reliability of BIOTRONIK's Plexa lead, as used in conjunction with a US market released BIOTRONIK implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) pulse generator. The evaluation of safety will be based on the analysis of Plexa lead-related adverse events. The Plexa Registry will provide data to permit characterization of Plexa lead failures contributing to loss of bradycardia pacing or shock therapy. Additionally, acute and chronic Plexa lead parameters will be evaluated.
Subject Population:	Subjects who are indicated for an ICD or a CRT-D. Subjects must be successfully implanted with a compatible US market released BIOTRONIK ICD or CRT-D. Subjects can be enrolled no more than 30 days after successful implantation of the Plexa system.
Enrollment:	This registry is designed to follow 1271 subjects implanted with the Plexa system through 5 years post-implant.
Clinical Sites:	Up to 75 US sites.
Primary Endpoint:	Overall incidence of adverse events (AEs) related to the Plexa lead
Secondary Endpoints:	1. Incidence of each individual type of AE that contributes to Primary Endpoint 1 2. Pacing threshold, sensing, and impedance measurements for the Plexa lead through 5 years post-implant 3. Shock impedance for the Plexa lead through 5 years post-implant 4. AE rates for AEs excluded from primary safety endpoint 1, through 5 years post-implant
Clinical Events Committee Chair:	Dr. Gábor Duray State Health Center Róbert Károly krt. 44 1134 Budapest Hungary
Sponsor:	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035

1. INTRODUCTION

1.1 NAME OF DEVICE

This protocol details the registry for BIOTRONIK's Plexa implantable cardioverter defibrillator (ICD) lead, further referred to as the Plexa lead throughout this document. Currently, the following models are FDA approved:

- Plexa SD (active fixation, DF4 connector, dual coil),
- Plexa S (active fixation, DF4 connector, single coil),
- Plexa DF-1 SD (active fixation, DF-1 connector, dual coil),
- Plexa DF-1 S (active fixation, DF-1 connector, single coil), and
- Plexa DF-1 S DX (active fixation, DF-1 connector, single coil with atrial sensing channel).

1.2 REGISTRY OVERVIEW

The purpose of this registry is to confirm the safety and reliability of the Plexa lead as used in conjunction with any compatible US market released BIOTRONIK ICD or cardiac resynchronization therapy defibrillator (CRT-D). Data will be collected from no more than 1271 subjects from implant through 5 years of follow-up.

Subjects eligible for the registry include those that have been successfully implanted with a Plexa lead and a compatible US market released BIOTRONIK ICD or CRT-D no more than 30 days prior to enrollment*. Prior to enrollment procedures, subjects will be screened to ensure eligibility and will provide written informed consent. Safety will be evaluated based on the analysis of all Plexa lead-related adverse events. Acute and chronic lead parameters for sensing, pacing thresholds, pacing impedance, and shock impedance will be evaluated for the Plexa lead.

All devices included in the registry are legally marketed and prescribed by physicians according to approved indications for use.

1.3 BACKGROUND

The Plexa Registry is designed to document the clinical experience of the Plexa ICD leads (P98023/S075, approved January 5, 2017).

The Plexa lead is a transvenous ICD lead designed for permanent right ventricular pacing, sensing, and delivery of defibrillation / cardioversion shock therapies to the heart. Plexa is the successor of the Linox^{smart} and Protego ICD lead (Linox^{smart} SD / TD P980023/S038, approved September 17, 2010; Linox^{smart} S / T P980023/S043, approved February 28, 2011; Linox^{smart} S DX P980023/S049, approved February 13, 2013; Protego S / SD / T / TD P980023/S057, approved July 3, 2014). The Linox lead family has been extensively studied in the GALAXY registry. The Protego DF4 lead is being studied in the ongoing Protego DF4 Post-Approval Registry.

* For the purpose of the Plexa registry, the date of implant will be considered day 0.

1.3.1 GALAXY Lead Registry: Clinical Experience with Linox ICD Lead

BIOTRONIK sponsored the GALAXY study, an after-market registry to confirm the long-term safety and reliability of the FDA approved Linox family of ICD leads. The GALAXY Registry is registered on clinicaltrials.gov, NCT00836589. This multi-center, prospective, non-randomized registry has been ongoing since enrollment began in January 2009 and has been closed to enrollment since November 2011. The final subject visit occurred in December 2016 and the final clinical report is pending. There were 1997 subjects enrolled in the registry, 201 of which were implanted with Linox^{smart} ICD leads.

The sensing and pacing behavior was evaluated as well as the rate of lead-related complications over the available follow-up period. As of November 3, 2015, the mean pacing threshold across all Linox family ICD lead models was 0.64 ± 0.35 V, the mean sensing amplitude was 12.79 ± 5.44 mV, and the mean lead impedance was 553.0 ± 134.9 ohms. There were 61 (3.05%) subjects who experienced a primary AE related to the Linox family ICD leads.

Details on reported ICD lead-related adverse events are provided in Table 1. The total number of subjects with an adverse event may not equal the sum of the number of subjects listed in each category because an individual subject may have experienced more than one adverse event.

Table 1: All Linox Family ICD Lead-Related Adverse Events

Adverse Event	Subjects with AE, n	% Subjects with AEs	AEs, n
Primary Endpoint AEs			
Other ICD lead related: Lead noise or oversensing	21	1.05%	21
Lead impedance out of range, low impedance, potential insulation break.	16	0.80%	16
Lead impedance out of range, high impedance, potential conductor fracture.	15	0.75%	15
Lead dislodgement (> 180 days post-implant procedure)	6	0.30%	6
Lead undersensing or loss of sensing	2	0.10%	2
Inability to defibrillate or pace	1	0.05%	1
Other ICD lead related: Noise consistent with probable fracture	1	0.05%	1
Other ICD lead related: Lead migrated	1	0.05%	1
Other ICD lead related: Tension pneumothorax	1	0.05%	1
Total Primary Endpoint AEs	*61*	*3.05%*	*64*
Secondary Endpoint AEs Related to the ICD Lead			
Lead dislodgement (≤ 180 days post-implant procedure)	24	1.20%	25
High pacing threshold, intermittent capture, no lead capture	13	0.65%	14
Cardiac perforation with or without tamponade	5	0.25%	6
Total Secondary Endpoint AEs (Related to ICD Lead)	*42*	*2.10%*	*45*
Total Primary or Secondary AEs (Related to ICD Lead)	**100**	**5.01%**	**109**

Total number of subjects = 1997

Figure 1 shows the calculated Kaplan-Meier actuarial graph demonstrating the freedom from all primary endpoint adverse events adjudicated by the Clinical Events Committee. Table 2 displays the associated case summary. A common, final follow-up date of November 3, 2015, is assumed for all active subjects.

The standard error (SE) for the estimated survival (freedom from primary endpoint AEs) was calculated using the method of Peto et al[1]. The last adverse event occurred on day 1809, and the current estimated freedom from adverse events is 95.0% (SE 1.0%) for implant times 1809 days or longer. These estimates may change as additional follow-up data are collected.

Figure 1: GALAXY Freedom from Primary Endpoint Adverse Events (%)

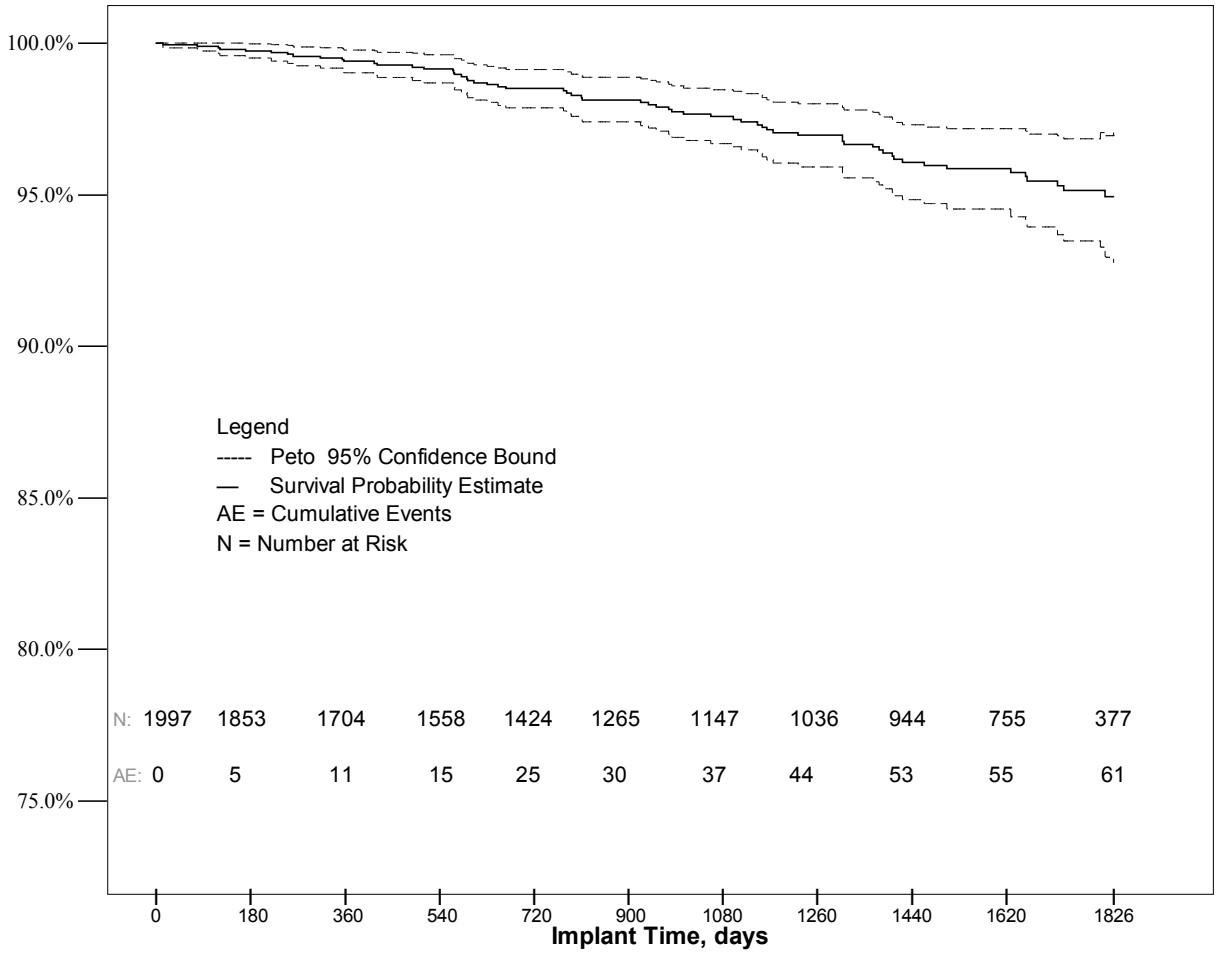


Table 2: GALAXY Primary Endpoint Case Summary

Total Subjects, n	Subjects with Adverse Events, n	Censored	
		n	%
1997	61	1936	96.9%

1.3.2 Protego Lead Registry: Clinical Experience with Protego ICD Lead

BIOTRONIK is currently conducting the Protego Post-Approval Registry to confirm the long-term safety and reliability of the FDA approved Protego DF4 ICD leads. The Protego Post-Approval Registry is registered on clinicaltrials.gov, NCT02243696. This multi-center, prospective, non-randomized registry has been ongoing since enrollment began in September 2014 and has been closed to enrollment since October 2016. There have been 1695 subjects enrolled in the registry as of October 10, 2016.

As of May 31, 2016, the sensing and pacing behavior was evaluated as well as the rate of lead-related complications over the available follow-up period. The mean pacing threshold across all Protego family ICD lead models was 0.62 ± 0.34 V, the mean sensing amplitude was 15.68 ± 6.00 mV, and the mean lead impedance was 574.8 ± 122.3 ohms. There was one (0.08%) subject who experienced a primary AE reported as related to the Protego ICD lead and 16 (0.23%) subjects who experienced a secondary AE reported as possibly related to the Protego ICD lead (Table 3). No subjects experienced a secondary AE adjudicated as related to the Protego ICD lead.

Table 3: Protego ICD Lead-Related Adverse Events

Adverse Event	Subjects with AE, n	% Subjects with AEs	Number of AEs
Primary Endpoint AEs			
Lead dislodgement (> 30 days post-implant procedure)	1	0.08%	1
Total Primary Endpoint AEs	*1*	*0.08%*	*1*
Secondary Endpoint AEs Possibly Related to the ICD Lead			
Lead dislodgement (≤ 30 days post-implant procedure)	7	0.54%	7
High pacing threshold	3	0.23%	1
Bent connector pin noted during implant procedure	1	0.08%	1
Cardiac perforation	1	0.08%	1
Inability to extend helix during implant procedure	1	0.08%	1
Intermittent capture / no lead capture	1	0.08%	1
Lead impedance out of range, high impedance	1	0.08%	1
Lead undersensing or loss of sensing	1	0.08%	1
Total Secondary Endpoint AEs (Possibly Related to ICD Lead)	*16*	*0.23%*	*16*
Total Primary or Secondary Endpoint AEs (Possibly Related to ICD Lead)	**17**	**1.30%**	**17**

Total number of subjects = 1305

Figure 2 shows the calculated Kaplan-Meier actuarial graph demonstrating the freedom from all primary endpoint adverse events adjudicated by the Clinical Events Committee. Table 4 displays the associated case summary. A common, final follow-up date of May 31, 2016, is assumed for all active subjects.

The standard error (SE) for the estimated survival (freedom from primary endpoint AEs) was calculated using the method of Peto et al[1]. The last adverse event occurred on the day of implant, and the current estimated freedom from adverse events is 99.91% (SE 0.16%) for implant times 94 day or longer. These estimates may change as additional follow-up data are collected.

Figure 2: Protego Freedom from Primary Endpoint Adverse Events (%)

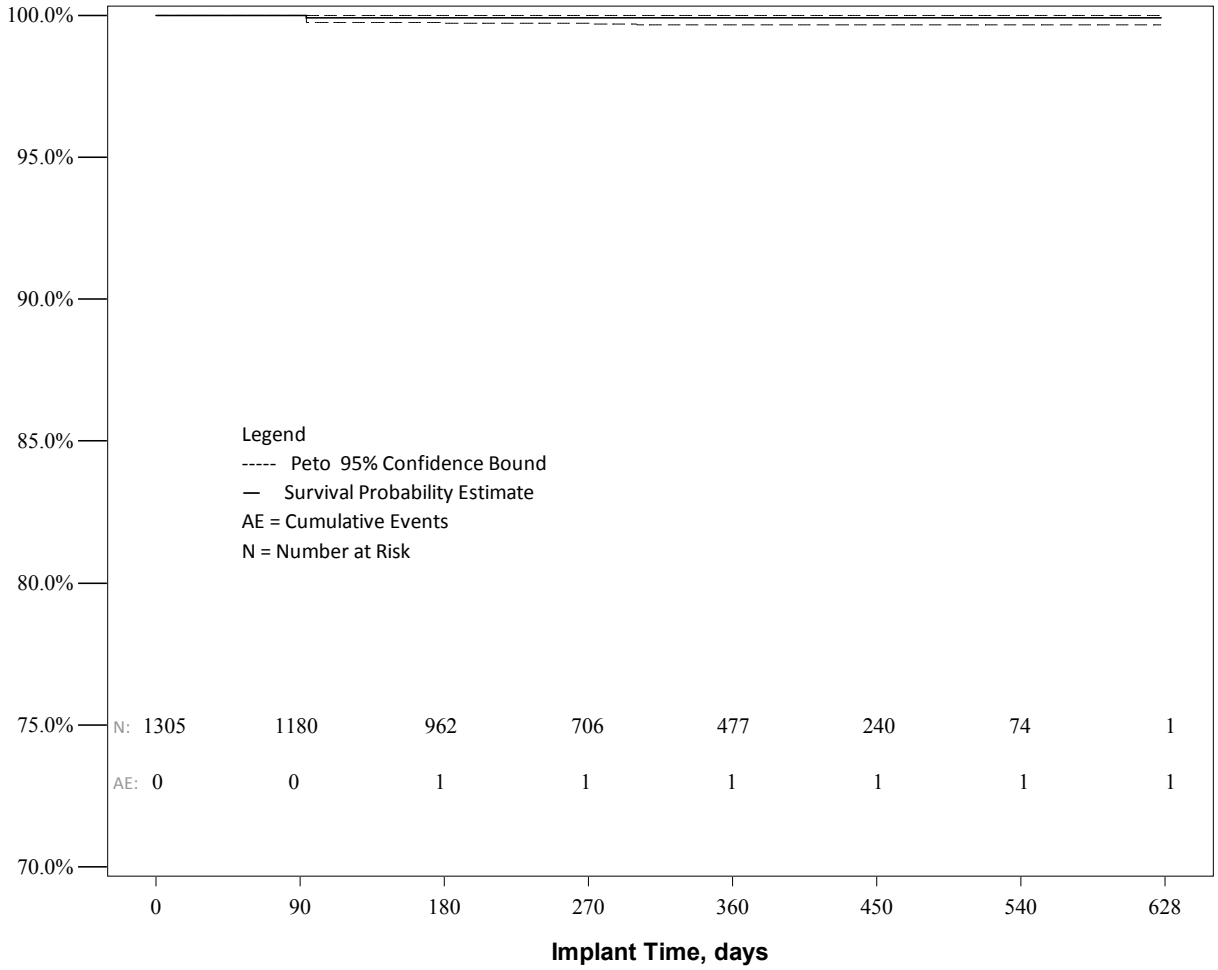


Table 4: Protego Primary Endpoint Case Summary

Total Subjects, n	Subjects with Adverse Event, n	Censored	
		n	%
1305	1	1304	99.9%

1.4 DEVICE DESCRIPTION

1.4.1 Plexa Lead Description

The Plexa leads are 7.8 F transvenous, steroid-eluting, endocardial lead for use with any ICD or CRT-D. The Plexa DF-1 S and Plexa S leads have two RV sensing and pacing electrodes (distal tip and ventricular ring electrode) and one defibrillation electrode (ventricular shock coil). The Plexa DF-1 S DX lead has two RV sensing and pacing electrodes, two RA sensing electrodes, and one defibrillation electrode (ventricular shock coil). The Plexa DF-1 SD and Plexa SD leads have two sensing and pacing electrodes (distal tip and ventricular ring electrode) and two defibrillation electrodes (ventricular and superior vena cava shock coils).

These leads, in conjunction with an ICD or CRT-D device, perform the following functions:

- Sense electrical signals from cardiac tissue and conduct those signals to the ICD
- Conduct bradycardia and anti-tachycardia pacing pulses emitted from the ICD to cardiac tissue
- Conduct cardioversion / defibrillation shocks of both high and low energies from the ICD to cardiac tissue

The Plexa leads are intended for permanent placement in the right ventricle. The tip and ring electrodes form the most distal portion of the lead and provide dedicated bipolar sensing and pacing.

All Plexa leads have one shock electrode that is positioned in the right ventricle. The Plexa DF-1 SD and Plexa SD dual-coil ICD leads have an additional shock electrode for placement in the superior vena cava (SVC). All Plexa leads feature Silglide® surface treatment, designed to reduce the force required to maneuver the lead during the implant procedure.

All Plexa leads feature an electrically active extendable / retractable fixation helix for use in lead placement. The helix is extended and retracted by rotating the contact pin with a fixation tool. Both the fixation helix and ring electrode are comprised of a platinum / iridium alloy base with fractal iridium.

The distal tip of all Plexa leads consists of a steroid eluting collar which contains the active ingredient dexamethasone acetate (DXA). Upon exposure to body fluids, the steroid elutes from the collar. 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.

The Plexa lead has a modified internal lead tip design, with a symmetric contact spring, and minor changes to the cut of the tip of the fixation screw as compared to the Linox^{smart} and Protego leads. Additionally, the distal region, between the proximal end of the RV shock coil and the distal end of the SVC shock coil has a twisted cable design, where the lumens of the cables (peripheral lumens) are twisted around the inner lumen of the coil (helically wound around the longitudinal axis). All five lumens are coated with a lubricant, compared to only four peripheral lumens in the Linox^{smart} and Protego leads. The color coding on the label tubing has been updated according to AAMI TIR41:2014. The steroid collar on the Plexa lead has a nominal value of 0.93 mg DXA.

1.4.2 BIOTRONIK Home Monitoring®

Current expert consensus advocates 3- to 6-month device evaluations either in-person or by remote monitoring for ICD or CRT-D devices[2].

BIOTRONIK Home Monitoring® is a communication system which allows the automatic transmission of diagnostic patient data from the device to the physician at any time. The technology implements the use of wireless communications to provide the physician with daily patient monitoring and trend analysis information between office follow-up visits. A block diagram of the transmission path is shown in Figure 3, and the transmission steps are described as follows:

1. Communication starts with the implant, which activates a very low power RF transmitter circuitry integrated within the pulse generator.
2. The patient's device accepts patient data from the implant and transfers this digital information using a cellular short messaging system (SMS) or telephone landline connection to a BIOTRONIK Service Center for evaluation.
3. The BIOTRONIK Service Center receives incoming data and generates a customized summary which is available to the physician online via secure Internet access, or can be forwarded to the physician via fax.

Figure 3: BIOTRONIK Home Monitoring® Transmission Path

BIOTRONIK conducted the TRUST study to evaluate the safety and effectiveness of BIOTRONIK Home Monitoring®. BIOTRONIK received FDA approval (P050023/S020, approved May 12, 2009) of the following labeling claims regarding BIOTRONIK Home Monitoring®:

1. BIOTRONIK Home Monitoring® information may be used as a replacement for device interrogation during in-office follow-up visits.
2. A strategy of care using BIOTRONIK Home Monitoring® with office visits when needed has been shown to extend the time between routine, scheduled in-office follow-ups of BIOTRONIK implantable devices in many patients. BIOTRONIK Home Monitoring® data is helpful in determining the need for additional in-office follow-up.
3. BIOTRONIK Home Monitoring® patients—who are followed remotely with office visits when needed—have been shown to have similar numbers of strokes, invasive procedures and deaths as patients followed with conventional in-office follow-ups.
4. BIOTRONIK Home Monitoring® provides early detection of arrhythmias.
5. BIOTRONIK Home Monitoring® provides early detection of silent, asymptomatic arrhythmias.
6. Automatic early detection of arrhythmias and device system anomalies by BIOTRONIK Home Monitoring® allows for earlier intervention than conventional in-office follow-ups.
7. BIOTRONIK Home Monitoring® allows for improved access to patient device data compared to conventional in-office follow-ups since device interrogation is automatically scheduled at regular intervals.

In current US market released BIOTRONIK ICD and CRT-D devices, BIOTRONIK Home Monitoring® provides event and system information similar to what is currently available during office follow-up visits. The highlighted information in the BIOTRONIK Home Monitoring® Quick View Summary Report, Figure 4, displays the study related follow-up data automatically transmitted on a daily basis including: battery status, pacing impedance, pacing threshold, and sensing amplitude (mean / min) for both the atrial and ventricular leads. In addition, BIOTRONIK Home Monitoring® provides automatic daily information on arrhythmias, lead trends, current device programming, event episodes, therapy provided, and long term data trends.

Figure 4: BIOTRONIK Home Monitoring® Quick View Summary Report

Device status	
Status	OK
Battery status	BOS (EOS, ERI, MOS2, MOS1, BOS)
Battery voltage	3.04 V (Jul 14, 2016)
Charge time	8.9 s for 40 J (Jun 13, 2016 12:46:45 AM)

Findings
No anomalies

Tachy settings	Zone limit	1st ATP	2nd ATP	1st shock	2nd shock	3rd - nth sho.
VT1	400 ms	OFF	OFF	OFF	---	---
VT2	350 ms	3 * Burst	OFF	40 J	40 J	6 * 40 J
VF	300 ms	Burst		40 J	40 J	6 * 40 J

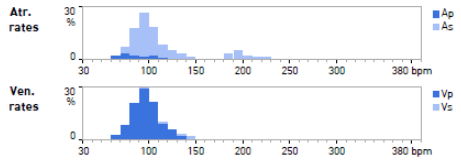
Brady / CRT / AF settings	
Mode	DDD-CLS / BiV-LV
Basic rate / UTR [bpm]	60 / 130
AV delay at 60 bpm / 130 bpm	190 / 160 ms
Mode switching	160 bpm / DDIR

Brady leads	RA lead	RV lead	LV lead
Pacing impedance [ohm]	535	665	911
Pacing threshold [V]	---	0.4	---
Sensing ampl. mean / min [mV]	5.8 / 5.4	13.0 / 12.4	> 20.0 / > 20.0
Programmed [V@ms]	3.5 @ 0.40	3.5 @ 0.40	3.5 @ 0.40

Shock lead	
Daily shock lead imp. [ohm]	66
Last delivered shock imp. [ohm]	---

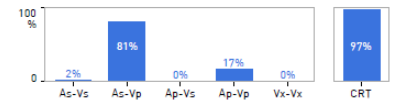
Ven. arrhythmias since Apr 15, 2016	VT1	VT2	VF
Therapy episodes	0	0	0
ATP started / succ.	0 / 0		0 / 0
Shocks started / aborted / succ.	0 / 0 / 0		
Last episode: SVT (Jul 12, 2016 9:43:24 AM)			

Rate histogram from Apr 14, 2016 until Jun 24, 2016



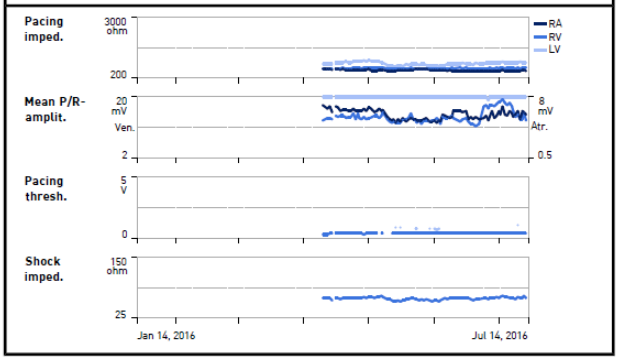
Atrial arrhythmias since Apr 15, 2016	
Atrial burden	0.0% of day
Mean ven. heart rate during atr. burden	---
Atrial arrhythmia ongoing at end of mon. interv.	NO
Atrial monitoring / therapy episodes	1 / OFF
Atrial therapies started / succ.	OFF
SVT episodes	22

Event episodes since Apr 15, 2016

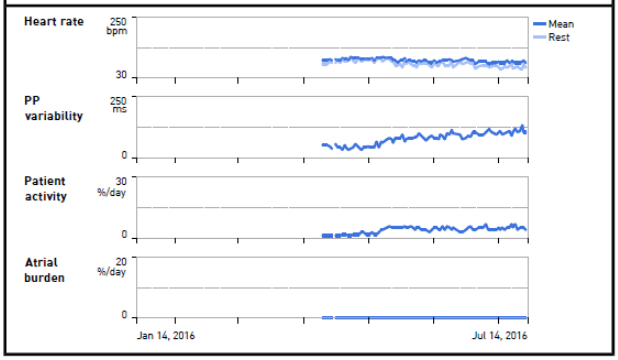


Pacing	
Ap	14%
RVp	97%
BiV	97%

Lead trends



Long term trends



2. REGISTRY DESIGN

This multi-center, prospective, non-randomized registry is designed to gather safety data on BIOTRONIK's Plexa leads. All subjects enrolled in the registry are implanted with a US market released BIOTRONIK ICD or CRT-D pulse generator and a Plexa lead.

Potential subjects will be identified by the investigator from their general patient population. Additionally, potential subjects must satisfy the registry inclusion and exclusion criteria (Section 3.1.3 and Section 3.1.4). After successful implantation of the Plexa lead with a US market released BIOTRONIK ICD or CRT-D pulse generator, if a subject satisfies the registry inclusion and exclusion criteria, written informed consent is obtained. After informed consent has been obtained, enrollment visit data will be collected. Informed consent and enrollment visit data collection may be obtained no more than 30 days after the date of implant. Device data and any adverse events since the date of the implant of the Plexa lead active at the time of consent will be collected retrospectively at the enrollment visit.

After enrollment, any subjects who have the pulse generator explanted or Plexa lead explanted or capped must be re-implanted, or have plans to be re-implanted, with a Plexa lead connected to a US market released BIOTRONIK pulse generator to remain in the study.

After enrollment, subjects will be evaluated at 3 months post-implant, 6 months post-implant, and every 6 months thereafter for 5 years. All subjects are required to be seen in-office once between the 24 and 36 month intervals and once at the 60 month interval. For all other visits, subjects may use BIOTRONIK Home Monitoring® follow-ups to meet the study visit schedule. The option to substitute a BIOTRONIK Home Monitoring® follow-up for an in-office follow-up may begin as early as the 3 month post-implant visit. Subjects should be seen in-office if not all information required during follow-up visits as noted in Section 3.2.4 can be obtained from BIOTRONIK Home Monitoring®. Subjects without a BIOTRONIK Home Monitoring® system should be seen in-office for all intervals per the study visit schedule.

Figure 5 provides an overview of the clinical registry design. Details of subject eligibility requirements are noted in Section 3.1 and details of other registry specific procedures and data collection are noted in Section 3.2 and Section 4. Figure 6 provides the visit schedule for a subject using BIOTRONIK Home Monitoring®.

BIOTRONIK may pool data from other prospective studies to supplement the Plexa Registry population to achieve the sample size of 1271 subjects needed for the primary endpoint analysis. The data collection would need to be sufficiently similar to the Plexa Registry data collection to allow pooling of the data. If data from other studies are used, the data will come from subjects who have a US market released BIOTRONIK ICD or CRT-D pulse generator and a successfully implanted Plexa lead.

Figure 5: Registry Design Flowchart

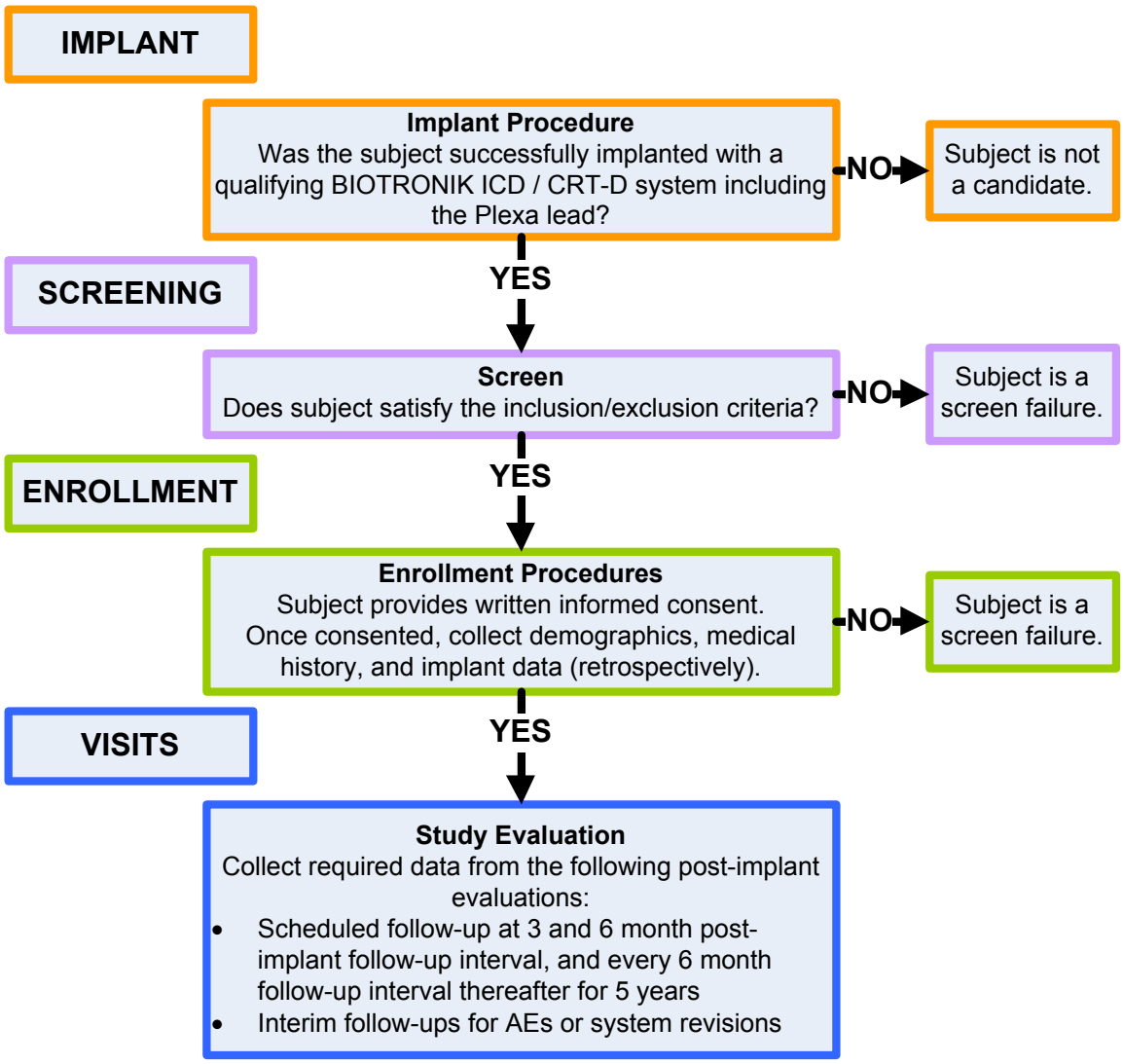
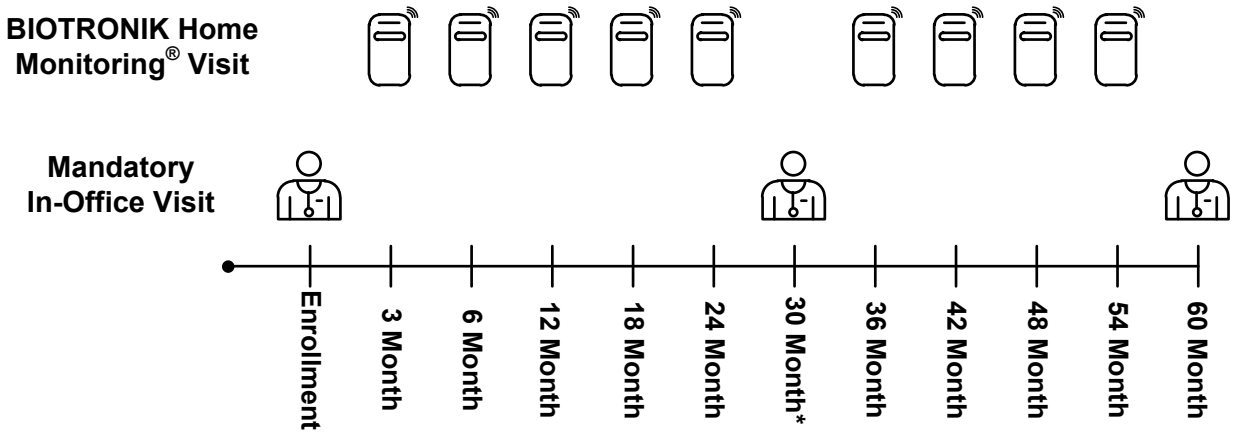


Figure 6: Visit Schedule



* In-office visit may be performed at 24, 30, or 36 Month interval

2.1 REGISTRY ENDPOINTS

This registry includes the assessments of one primary safety endpoint related to the Plexa lead and several secondary endpoints that evaluate the safety and effectiveness of the Plexa system.

2.1.1 Primary Endpoint 1

The purpose of primary endpoint 1 is to evaluate the overall incidence of adverse events related to the Plexa lead (as defined in Section 9) from implant through 5 years. Assuming that the expected Plexa lead adverse event rate at 5 year post-implant (proportion of subjects with at least one AE in the timeframe from implant through 5 year post-implant) is 7.5% or less, then the primary safety endpoint will be evaluated in the following testable hypothesis in superiority format.

H_o: The adverse event-free rate (AEFR) for subjects receiving the Plexa lead at 5 years post-implant is less than or equal to 92.5%

$AEFR \leq 92.5\%$

H_a: The adverse event-free rate (AEFR) for subjects receiving the Plexa lead at 5 year post-implant is greater than 92.5%

$AEFR > 92.5\%$

If the two-sided, 95% lower confidence bound is greater than 92.5%, then the null hypothesis will be rejected.

2.1.2 Secondary Endpoints

There are no formal tests of hypotheses associated with secondary endpoints 1-4.

1. Incidence of each individual type of AE that contributes to Primary Endpoint 1
2. Pacing threshold, sensing and impedance measurements for the Plexa lead through 5 years post-implant
3. Shock impedance for the Plexa lead through 5 years post-implant

4. Adverse event rates for protocol defined, Clinical Events Committee (CEC) adjudicated AEs excluded from primary safety endpoint 1, through 5 years post-implant

2.1.3 Additional Data of Interest

Additional information may be collected to characterize the registry population, implanted system, and progress of the registry. When available, the collected information may include baseline demographics, medical history, implanted system, system revisions, Plexa lead extractions, returned product analysis, and compliance. Specifically, data of interest may include:

- Baseline demographics, such as date of birth, gender, height, weight, and New York Heart Association (NYHA) class (if available)
- Medical history, including indication for device
- Implanted device data from initial implant and / or revisions, including implant dates and manufacturers for all implanted pulse generator and leads. Additionally, models and serial numbers will be collected for BIOTRONIK pulse generator and leads.
- Implant procedure data (collected retrospectively at enrollment)
- Revision procedure data (may be collected retrospectively)
- Plexa DX lead atrial dipole sensing measurement
- Results from returned product analysis
- Compliance to protocol requirements and registry visit schedule

2.2 REGISTRY SIZE AND DURATION

To document the clinical experience of the Plexa lead, the Plexa Registry is designed to follow 1271 subjects through the 60 month post-implant visit interval at up to 75 US sites.

2.3 SAMPLE-SIZE ANALYSIS

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

The estimated sample size required to evaluate primary endpoint 1 is based on a superiority comparison of the overall Plexa lead AE-free rate to 92.5% at 5 years. The sample size for primary safety endpoint 1 was calculated based on the following assumptions:

<u>Assumptions for primary safety endpoint 1</u>

- Registry Design: nonrandomized registry
- Test basis: exact binomial test
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Estimated AE-Free Rate at 5 years: 95.0% for Plexa leads
- Performance goal for AE-Free Rate at 5 years: 92.5%

For primary safety endpoint 1, a total of 750 evaluable Plexa leads would be required to demonstrate superiority to an AE-free rate of 92.5%. Assuming a 10% loss to follow-up rate per year over 5 years of follow-up (average of 8.2% of original population per year), a total of 1271 (= 750 / 0.9^5) subjects with an ICD lead would be required to be enrolled to evaluate primary safety endpoint 1.

2.3.1 Attrition

For the sample size calculation, a maximum loss to follow-up of 10% per year (41% over 5 years) was assumed. The attrition rate encompasses all causes for subject exits prior to study completion and will include any subject exits where the subjects are not replaced per Section 2.3.2.

2.3.2 Replacement of Subjects

A drop-out rate of 10% of subjects per year is expected in the Plexa Registry. The additional enrollment of 10% (total subject number: n = 750 / 0.9^5) is considered sufficient for the collection of the required primary endpoint 1 (n = 750). However, to ensure sufficient primary endpoint 1 evaluable data, subjects who exit the clinical investigation due to death, device explants, subject directed withdrawals, physician directed withdrawals, or loss of contact with the subject may be replaced as long as enrollment is ongoing. Subjects who have had a protocol defined adverse event will not be replaced. The subjects replaced will not count towards the overall planned subject number of 1271.

2.4 DATA ANALYSES

The analysis population for the primary endpoint in the registry will be the intention-to-treat (ITT) population. This population analysis will include all subjects who provided informed consent,met the enrollment criteria, and completed the five year follow-up period or exited the trial early with a primary endpoint event.

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.

2.4.1 Endpoint Analysis

Primary safety endpoint 1 will be evaluated by performing an exact binomial test comparing the observed proportion (overall AE-free rate at 5 years) to 92.5%. The lower bound of the 95% confidence interval must be greater than 92.5%.

The evaluation of secondary safety endpoint 1 will be based on the exact, two-sided 95% confidence interval for the observed, individual AE rates at 5 years. Secondary endpoints 2 and 3, which summarize pacing thresholds, sensing, impedance measurements and shock impedance measurements for the Plexa lead, will be reported via standard measures, which can include means, standard deviations, medians, minimums, and maximums.

Secondary endpoint 4, which includes AEs that were excluded from primary safety endpoint 1, through 5 years post-implant will also be summarized as AE rates together with their associated, exact 95% confidence intervals.

2.4.2 Trend Analyses

The primary safety endpoint is evaluated at 5 years post-implant against pre-specified performance levels (92.5% for overall freedom from Plexa lead-rated AEs). To monitor the ongoing incidence of any potential AEs against the accumulating follow-up exposure post-implant, Kaplan-Meier survival curves may be prepared at the reporting intervals for Primary Endpoint 1. Root causes for any failures, regardless of the incidence rates, may be investigated.

2.4.3 Missing Data

All possible steps will be taken to minimize missing data in the registry. This includes but is not limited to monitoring of registry electronic case report forms (eCRFs) for completeness and supporting efforts to track and maintain contact with registry subjects during the follow-up period.

The reasons for any missing data in the registry should be documented. BIOTRONIK Home Monitoring® can provide daily automatic sensing values, pacing thresholds, shock impedance, and pacing impedance, depending on the device programming. When available, missing data will be imputed with BIOTRONIK Home Monitoring® values obtained from the day of a completed follow-up, target date of a missed follow-up, or the next closest day in the visit window.

For evaluation of primary endpoint1, only subjects who achieve 5 years of follow-up or have experienced an adverse event prior to 5 years will be included in the final evaluation of the associated hypotheses. The secondary endpoints 1 and 4 of other AEs at 5 yearswill be analyzed in a similar manner. There will be no imputation for these missing adverse event outcomes.

For purposes of the final report Kaplan-Meier survival analyses, all AE data on enrolled non-replaced subjects will be included with follow-up times censored at the time of exit or last completed study visit representing the time of the last known AE status.

Secondary endpoints 2 and 3, which include pacing thresholds, sensing, pacing impedance, and shock impedance measurements will be summarized by scheduled visit through the 5 years of registry follow-up

2.4.4 Poolability Analysis

The distribution in AE-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.

Additionally, a Cochran-Mantel-Haenszel test with continuity adjustment will be used to assess the poolability of data collected across the different 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.

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 subject selected for participation should be from the investigator's general patient population according to the inclusion and exclusion criteria described below.

3.1.1 Indications

The Plexa steroid-eluting, bipolar transvenous lead system is intended for use in the right ventricle of patients for whom implantable defibrillators are indicated. For this registry, the Plexa lead is utilized in conjunction with any US market released ICD or CRT-D device.

3.1.2 Contraindications

Do not use the Plexa lead system in patients with severe tricuspid valve disease or patients who have a mechanical tricuspid valve implanted. The Plexa steroid-eluting leads are contraindicated for patients who cannot tolerate a single systemic dose of up to 1.02 mg dexamethasone acetate (DXA).

3.1.3 Inclusion Criteria

To support the objectives of this investigation, the inclusion criteria at the time of subject enrollment for this registry include the following requirements:

- Successfully implanted with a BIOTRONIK ICD or CRT-D compatible system along with the Plexa lead no more than 30 days prior to consent[†]
- Able to understand the nature of the registry and provide informed consent
- Available for follow-up visits on a regular basis at the study site for the expected 5 years of follow-up
- Accepts BIOTRONIK Home Monitoring® concept
- Age greater than or equal to 18 years

3.1.4 Exclusion Criteria

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

- Enrolled in any investigational cardiac device trial
- Enrolled in BIOTRONIK's QP ExCELs lead study
- Planned cardiac surgical procedures or interventional measures within the next 6 months
- Expected to receive heart transplantation or ventricular assist device within 1 year
- Life expectancy of less than 1 year
- Patients reporting pregnancy at the time of enrollment

[†] Sponsor may approve a site specific waiver upon written request to allow enrollment prior to implant per institution's requirements.

3.2 REGISTRY PROCEDURES

Subjects will be enrolled no more than 30 days from implant of a BIOTRONIK ICD or CRT-D device and Plexa lead. BIOTRONIK Home Monitoring® should be activated in subjects who have a BIOTRONIK Home Monitoring® system. BIOTRONIK Home Monitoring® data can be utilized to assist in triage and diagnosis of lead-related adverse events between scheduled follow-ups. All subjects are required to be seen in-office once between the 24 and 36 month intervals and once at the 60 month interval. For all other visits, subjects may use BIOTRONIK Home Monitoring® follow-ups to meet the study visit schedule. Subjects without a BIOTRONIK Home Monitoring® system should be seen in-office for all intervals per the study visit schedule.

Registry Procedure Visits:

- Implant (collected retrospectively during enrollment)
- Enrollment
- Routine follow-up evaluations at 3 months post-implant, 6 months post-implant, and every 6 months thereafter for 5 years
- Interim follow-up information is only collected in support of AEs and is not required to be entered as a visit in the EDC
- System revision (if applicable)

Table 5 summarizes the visit assessment schedule.

Table 5: Registry Visit Assessment Schedule

	Implant[1]	Enrollment	Routine Follow-up Intervals[2]	Interim Evaluation[3]	System Revision
Informed consent		X			
Demographics and medical history[1]		X			
Implant information[1]	X[1]	X[1]			X[1]
Device evaluation	X		X	X	X
Adverse event assessment	X	X	X	X	X
Complete eCRFs	X	X	X	X	X

[1] Data may be collected retrospectively. Implant data is collected retrospectively at the enrollment visit. Implant information is also collected at system revisions regardless of the location of the procedure. Demographics and medical history information may also be collected retrospectively during the enrollment visit.

[2] 3, 6 months post-implant and every 6 months thereafter for 5 years post-implant. All subjects are required to be seen in-office once between the 24 and 36 month intervals and once at the 60 month interval. For all other visits, subjects may use BIOTRONIK Home Monitoring® follow-ups to meet the study visit schedule. Subjects without a BIOTRONIK Home Monitoring® system should be seen in-office for all intervals per the study visit schedule.

[3] Interim follow-up information is only collected in support of AEs and is not required to be entered as a visit in the EDC.

3.2.1 Registry Pre-Screening

Prior to enrollment, the patient's medical history must be reviewed in order to ensure the patient is an appropriate candidate for the registry. In addition, all patients must satisfy the registry inclusion and exclusion criteria prior to enrollment, including having been implanted with a Plexa lead and BIOTRONIK ICD or CRT-D no more than 30 days before consent.

3.2.2 Plexa Lead Implant

Implant information is collected retrospectively during the enrollment visit. Implant details and device data will be collected retrospectively as follows:

- Implant information
  - Date of implant
  - Implantation site (right or left) and, if available, implant approach (e.g. subclavian, axillary, etc.)
- Information on implanted system (pulse generator and leads manufacturer / model, serial numbers, etc.)
- Electrical parameters of the Plexa lead (if available, at least one pacing threshold measurement for each lead at 0.4 ms pulse width)
- Any lead-related, pulse generator-related and procedure-related adverse events occurring during implant

3.2.3 Enrollment Visit

If the patient has been determined to be eligible for the registry, informed consent must be obtained from the patient prior to initiating any registry related data collection. The consent process, including discussion of the registry, should be documented in the patient's medical record. A subject with a successfully implanted Plexa lead is considered enrolled in the registry upon signing the Informed Consent Form. The visit at which informed consent is obtained is the enrollment visit and occurs no more than 30 days after the date of implant. The system the subject has at the time of signing the Informed Consent Form will be considered the study system. Prior implanted systems will not count as part of the study and AEs will only be collected from the time of the study system implant. Subject demographics are to be obtained at the enrollment visit; however, some information may be historical if it is not available with proper source documentation.

The following data collection and reporting procedures are performed at the enrollment visit:

1. Obtain informed consent
2. Collect subject demographics (date of birth, gender, etc.)
3. Collected medical history of subject, including device implant indications
4. Obtain data from the implant procedure as outlined in Section 3.2.2
5. Perform routine device interrogation:
   - Determine ICD lead mean R-wave sensing amplitude
   - Determine ICD lead pacing threshold at 0.4 ms pulse width
   - Determine the ICD lead pacing impedance
   - Determine the ICD lead shock impedance

- If Plexa DX ICD lead, determine atrial dipole mean P-wave amplitude
- Enable BIOTRONIK Home Monitoring® (if not already enabled)
- Enable RV automatic threshold management (ATM) or RV ventricular capture control (VCC)

6. Complete all required eCRFs

3.2.4 Routine Follow-ups

Subjects will undergo an assessment of their implanted system 3 months (± 30 days) post-implant, 6 months (± 45 days) post-implant, and every 6 months (± 45 days) thereafter for 5 years. All subjects are required to be seen in-office once between the 24 and 36 month intervals and once at the 60 month interval. For all other visits, subjects may use BIOTRONIK Home Monitoring® follow-ups to meet the study visit schedule. Subjects without a BIOTRONIK Home Monitoring® system should be seen in-office for all intervals per the study visit schedule. Figure 6 provides the visit schedule for a subject using BIOTRONIK Home Monitoring®.

Each site Principal Investigator (PI) will be trained to identify and schedule follow-ups to meet the required visit expectation. Additionally, the electronic data capture system (EDC) will provide assistance in identifying properly scheduled follow-ups according to this protocol.

The following data should be collected:

1. Perform routine device interrogation:
    - Determine ICD lead mean R-wave sensing amplitude
    - Determine ICD lead pacing threshold at 0.4 ms pulse width
    - Determine the ICD lead pacing impedance
    - Determine the ICD lead shock impedance
    - If Plexa DX ICD lead, determine atrial dipole mean P-wave amplitude
2. Determine if there have been any study defined adverse events (see Section 9)
3. Export and store the electronic device interrogation
4. Complete all appropriate eCRFs

The following data collection and reporting procedures are performed for a BIOTRONIK Home Monitoring® evaluation:

1. Check “Last message” date on Quick View page to ensure the visit occurred within the visit window
2. Review the data and save the Quick View page of the appropriate transmission
3. Determine if there have been any study defined adverse events (see Section 9)
4. Complete all appropriate eCRFs

3.2.4.1 Device Programming

If BIOTRONIK Home Monitoring® evaluations will be used for routine follow-up visits, atrial and / or ventricular capture control should be programmed to “ON” or “ATM,” and BIOTRONIK Home Monitoring® activated to allow collection and evaluation of pacing threshold data. If atrial and / or ventricular capture control is not programmed “ON” or “ATM,” the subject should be seen in-office for study visits. If the atrial and / or ventricular capture control is disabled automatically due to AF, high intrinsic rate, or other reason, the reason should be documented in the EDC system and if the reason is unable to be resolved, the subject should be seen in-office for study visits.

3.2.5 Interim Follow-ups

Interim follow-ups may occur anytime during the registry. Data collected during interim follow-ups should be the same as a routine in-office follow-up. Interim follow-up data is only collected in EDC in support of lead or system related AEs or system revisions and is not required to be entered as an interim follow-up in EDC. Other hospital or clinic visits that are unrelated to the device are not required to be collected.

3.2.6 System Revisions

For interim evaluations that involve a system revision (even if the Plexa lead is not directly affected), the following should be completed:

1. Collect implant information
    - Date of revision
    - Implant site (right or left) and if available implant approach (e.g. subclavian, axillary, etc.)
    - Implant location of pulse generator and implanted leads
    - Whenever possible, devices that are explanted should be returned to BIOTRONIK for analysis
2. Collect information on newly implanted system (pulse generator and leads manufacturer / model, serial numbers, etc.)
3. Record electrical parameters of the implanted leads (perform at least one pacing threshold measurement for each lead at 0.4 ms pulse width)
4. Record any lead-related, pulse generator-related and procedure-related adverse events during implant and complete the Adverse Event eCRF
5. Set programming parameters to best suit the needs of the subject
6. Complete System Revision eCRF, as applicable

If the Plexa lead is replaced with another Plexa lead attached to a US market released BIOTRONIK pulse generator, the subject may continue participation in the registry based on the original implant date and visit schedule. If the Plexa lead is explanted and the subject is not re-implanted or will not be re-implanted with a new Plexa lead attached to a US market released BIOTRONIK pulse generator, the subject will be withdrawn from the registry. See Section 10.2.3 for details on withdrawals due to lead or pulse generator extraction.

4. DATA COLLECTION

4.1 ELECTRONIC DATA CAPTURE (EDC)

MedNet Solutions Incorporated is a privately held company that specializes in web-based clinical data management technology. MedNet will host the EDC system and provide a secure environment that is accessible to authorized individuals through the internet. BIOTRONIK will implement a registry specific configuration using this software to meet the data collection requirements of the protocol. The EDC system is 21 CFR Part 11 compliant and is the platform for electronic case report form (eCRF) data entry, clinical data discrepancy resolution, and access to reports for BIOTRONIK, specified study sites, and any other parties authorized by BIOTRONIK.

4.2 ELECTRONIC CASE REPORT FORMS (eCRFS)

Original data will be collected at each study site and recorded into the EDC system, audited and monitored by BIOTRONIK, via completion of eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs.

Information from electronically delivered source data (e.g. programmers) will be captured and stored in a validated environment until the end of the registry.

Subject follow-up is required for all subjects enrolled in this clinical registry. The required follow-up visit dates are based on Plexa lead implant date, and are to be used for the calculation of the dates of the routine follow-up schedule. The following eCRFs will be available in the EDC system:

- Informed Consent
- Enrollment
- Implant
- Lead Values (used for implant lead values and revision lead values)
- Follow-up (3 month ± 30 days post-implant, 6 months ± 45 days post-implant, and every 6 months ± 45 days thereafter for 5 years)
- Adverse Event
- System Revision
- Study Termination
- Protocol Noncompliance

4.3 DATA QUALITY CONTROL

BIOTRONIK will review registry data. At any time, reports may be generated on data completion and missing data for each study site. An EDC system will be used to track received and expected follow-up data and eCRFs for each participant. This system provides the capability to monitor the status, volume, and disposition of data as well as to identify data completed, due, overdue, and backlogged. In addition, all registry data will undergo automatic edit and plausibility checks, which provide information to the study sites to help improve and maintain data quality control procedures, and is designed to detect inaccuracies and inconsistencies.

To ensure protocol compliance at all participating study sites, BIOTRONIK monitors will conduct centralized and / or on-site monitoring throughout the course of the registry.

To ensure compliance with federal regulations, internal policies and procedures, and the registry protocol, the EDC vendor will also be audited by BIOTRONIK or a BIOTRONIK representative during the course of the registry.

4.4 SUBJECT RETENTION

Although the registry sample size has been calculated with a 10% subject attrition rate per year (41% total in 5 years), subject retention in a 5 year registry may pose additional, unforeseen challenges. BIOTRONIK will provide additional tools to the sites in an effort to minimize the number of subjects that are lost to follow-up. The EDC system includes an overview of each subject's follow-up schedule, including the windows for each follow-up.

4.5 SUBJECT DATA CONFIDENTIALITY

All information sent to BIOTRONIK pertaining to each subject will be kept confidential at BIOTRONIK and is subject to FDA inspection. Source documents used to support endpoint adjudication by the CEC in the Plexa Registry will have all confidential subject and site identifiers redacted prior to transmission. Reports submitted to the physician or publications of registry results will not make any reference to subject names.

In order to verify the registry data and ensure registry integrity, monitors from BIOTRONIK, the FDA, and the reviewing Institutional Review Board (IRB) may review and / or copy the registry records

5. RISKS AND RISK MINIMALIZATION

All devices included in this registry are legally marketed and being prescribed by physicians according to FDA approved indications for use. Additionally, all visits in this registry are standard of care. There are no new risks associated with participation in this study. Please refer to the product manuals for risks associated with the implanted leads, ICDs, or CRT-Ds.

6. REGISTRY ORGANIZATION

6.1 SPONSOR

BIOTRONIK is the "sponsor" of the Plexa Registry. A "sponsor" is defined as an entity that initiates, but does not conduct, an investigation. BIOTRONIK'S responsibility as the clinical study sponsor is to ensure protocol and regulatory compliance through proper monitoring of the investigation. As the investigator, the physician is responsible for conducting the study in accordance with the signed agreement, the protocol, applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB. The principal investigator must also accept responsibility for all aspects of the study including the actions of any co-investigators participating in the study at the study site.

6.2 CLINICAL EVENTS COMMITTEE

A Clinical Events Committee (CEC) consisting of at least 3 independent electrophysiologists will review and adjudicate adverse events that occur during the registry. The CEC will be blinded to the clinical registry site and subject identity, and to minimize bias, members will not participate as investigators. The CEC will create a registry specific charter defining the adverse event adjudication process, specifically detailing review guidelines along with appropriate response timelines.

All protocol defined adverse events included in the primary and secondary endpoint analysis (see Section 9.3.1 and Section 9.3.2) will be adjudicated by the CEC. The CEC will indicate whether the adverse event is related, possibly related, not related, or has an unknown relation to the Plexa lead. The CEC will have the responsibility to adjudicate the classification of each reported adverse event as implant procedure, implanted pulse generator, lead, or non-procedure non-system related, to adjudicate the category of AE (e.g. Plexa lead dislodgement, major hematoma, etc.), and to assess the seriousness of each AE.

7. REGISTRY MONITORING

7.1 SUMMARY

BIOTRONIK's responsibility as the clinical registry sponsor is to ensure protocol and regulatory compliance through proper monitoring of the investigation. BIOTRONIK requires IRB review and a subject Informed Consent Form for all after-market research. Monitoring may be conducted on-site at the study site or remotely by BIOTRONIK monitors.

Through on-site or centralized monitoring, BIOTRONIK will assess the site's performance in the following areas:

- Verification that informed consent was obtained
- Adherence to protocol eligibility criteria and requirements
- Conduct and documentation of procedures and assessments related to:
  - Study endpoints
  - Protocol required safety assessments
  - Evaluating, documenting, and reporting AEs, subject deaths, and withdrawals, especially when a withdrawal may be related to an adverse event.
- Investigator oversight and delegation of authority to study personnel
- Verification of study-specific required documentation
- Conduct and documentation of procedures essential to trial integrity
- Adherence to the applicable FDA regulations regarding the obligations of the investigator and maintenance of records.

As the investigator, the physician is responsible for conducting the registry in accordance with the signed agreement, the protocol, applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB. The principal investigator must also accept responsibility for all aspects of the registry including the actions of any sub-investigators participating in the registry at the study site.

7.2 REGISTRY MONITORS

Study monitors are trained, qualified, and designated by BIOTRONIK management to oversee the progress of an investigation at the study site. Additional monitors may be appointed as necessary.

The address to submit registry information to BIOTRONIK is:

BIOTRONIK, Inc.
Clinical Studies Department
6024 Jean Road
Lake Oswego, Oregon 97035

For technical assistance 24 hours a day, call:
(800) 547-0394

7.3 ON-SITE MONITORING VISITS

A monitor will conduct monitoring visits at study sites in accordance with the Monitoring Plan. Sites are required to support these visits and the study monitoring effort. On-site monitoring visits will also provide an assessment of the continued acceptability of the facilities to continue participation in the registry.

7.4 CENTRALIZED MONITORING

Centralized monitoring will be conducted throughout the course of the study in accordance with the Monitoring Plan. Some examples of data that may be monitored remotely include un-redacted, signed informed consent forms, enrollment, implant information, device data, adverse events reported in the EDC system, etc. Sites are required to support centralized monitoring by providing source documents to BIOTRONIK in order to source data verify data reported in the EDC system and resolving queries in a timely manner.

8. REGISTRY COMPLETION

BIOTRONIK will notify the registry site upon completion or termination of the registry or investigator's participation in the registry. At BIOTRONIK's request, an investigator will return any pertinent information in their possession. Whenever possible, BIOTRONIK will provide a final report to each study site that has closed since the previous report. Upon termination of this registry, BIOTRONIK personnel may conduct a registry closure visit according to the Monitoring Plan. If a closure visit occurs, during the visit, BIOTRONIK will verify registry records and ensure that the investigator understands any applicable regulatory requirements including those related to record retention. The investigator must retain records related to the registry for a period of 2 years after the registry is completed.

In the event that the registry is suspended or terminated, the investigator must inform all enrolled subjects who at that time have not yet exited the registry. Standard patient care will be ensured by the study site.

9. ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended event that occurs during the course of the study. The investigator will be required to assess and classify each reported adverse event as related to either the implant procedure, implanted pulse generator, Plexa lead, RV lead (separate from Plexa lead), right atrial lead, left ventricular lead, or as non-procedure non-system related. All reportable adverse events occurring after informed consent are collected. Reportable adverse events occurring prior to consent will only be collected beginning from the date of implant of the study system (the Plexa system active at the time of enrollment).

The study site should report each adverse event via an Adverse Event eCRF and if the IRB is notified, provide a copy of the IRB adverse event notification to BIOTRONIK.

9.1 REPORTABLE ADVERSE EVENTS

The following AEs (sorted by classification) will be reported if they meet the definition of a primary or secondary endpoint as defined in Section 9.3. The classifications listed below are general classifications for site reporting purposes. Detailed information for some classifications is located in Appendix A. The CEC charter may include alternate classifications for some adverse events.

9.1.1 Implant Procedure-Related Adverse Events

An AE will be classified as procedure-related if any one of the following occurred as a result of the implant procedure:

- Arrhythmias associated with the implant procedure
- Cardiac perforation with or without tamponade
- Coronary sinus dissection
- Damage to lead during procedure (e.g. accidental cut to lead body during pocket revision, device replacement, etc.)
- Incorrect lead connection with pulse generator
- Lead dislodgement during a procedure (e.g. during pocket revision, device replacement, etc.)
- Loose set-screw
- Major hematoma
- Non-healing pocket dehiscence requiring intervention
- Pneumothorax associated with the implant procedure
- Primary infection
- Pulmonary embolism associated with the implant procedure
- Venous occlusion associated with the implant procedure
- Other major implant procedure related adverse event

9.1.2 Pulse Generator-Related Adverse Events

An AE will be classified as pulse generator-related if any one of the following occurred:

- Inability to defibrillate or pace

- Premature battery depletion
- Pulse generator failure
- Pulse generator migration
- Skin erosion
- Other pulse generator related adverse event

9.1.3 Lead-Related Adverse Events

An AE will be classified as lead-related if any one of the following occurred:

- Abnormal defibrillation impedance
- Abnormal pacing impedance
- Cardiac perforation occurring post-implant
- Extracardiac stimulation
- Failure to capture / intermittent capture
- Failure to sense / undersensing
- High pacing threshold
- Lead conductor fracture
- Lead dislodgement
- Lead insulation breach
- Lead oversensing due to external noise
- Lead oversensing not due to external noise
- Lead-related thrombosis
- Other lead-related adverse event (not specified above)

9.1.4 Non-Procedure Non-System Related Adverse Events

An AE will be classified as non-procedure non-system related if any of the following occur and require a system revision or explant:

- Ablation sequelae
- Secondary infection
- Twiddler's syndrome
- Other non-elective invasive intervention

9.2 ENDPOINT ANALYSIS

All protocol defined adverse events included in the primary and secondary endpoint analysis will be adjudicated by the Clinical Events Committee (CEC) (see Section 2.1, Section 6.2, and section 9.3). For each adverse event, the CEC will indicate whether the adverse event relatedness to the Plexa lead is: not related, related, possibly related, or unknown.

In evaluation of primary endpoint 1 and secondary endpoint 1 for the registry, the estimates of AE rates will be based on the number of subjects with at least one “related” AE as a proportion of total subjects. Subjects with a final adjudicated related AE classification of “possibly related”, “not related” or “unknown” will not have that individual event contribute to or be included in the evaluation of primary safety endpoint. The same rules will be used for purposes of Kaplan-Meier survival analyses, described in Section 2.4.2.

Secondary endpoint 4, which includes AEs that were excluded from primary safety endpoint 1 through 5 years post-implant, will also be summarized as AE rates along with their associated, exact 95% confidence intervals.

9.3 ADVERSE EVENTS FOR THE ANALYSIS OF THE PRIMARY AND SECONDARY ENDPOINTS

9.3.1 Adverse Events for the Analysis of Primary Endpoint 1 and Secondary Endpoint 1

If any of the following invasive interventions occur in order to resolve an above listed Plexa lead-related AE, the AE will be included in the primary safety endpoint analysis:

- Lead surgically repositioned
- Lead surgically explanted
- Lead surgically replaced
- Lead surgically abandoned
- Other lead-related surgery performed

Additionally, if any of the following non-invasive interventions occur in order to resolve an above listed Plexa lead-related AE, the Plexa lead-related AE will be included in the primary endpoint analysis:

- Lead pacing polarity or pacing mode reprogrammed in response to a problem with the mechanical or electrical integrity of the lead
- Lead programmed off in response to a problem with the mechanical or electrical integrity of the lead
- Lead use continued based on medical judgment despite a known clinical performance issue

AEs that are corrected by reprogramming the pulse generator (other than the above) and resolved without invasive intervention will not be considered an adverse event. For example, electrical reprogramming of the pacing polarity to eliminate extracardiac stimulation will not be considered an adverse event if not in response to a problem with the mechanical or electrical integrity of the lead. Similarly, increasing pacing output as a result of an elevated threshold without further intervention will not be considered an adverse event.

Subject deaths as a result of a Plexa lead-related AE will be included in the primary endpoint analysis.

Primary endpoint 1 and secondary endpoint 1 will exclude 1) lead dislodgements that occur less than or equal to 30 days after lead implant or a lead revision procedure and 2) high pacing threshold, failure to capture, or intermittent capture that occurs less than or equal to 30 days after lead implant or a lead revision procedure. However, these will count towards secondary endpoint 4.

9.3.2 Adverse Events for the Analysis of Secondary Endpoint 4

All major implant procedure-related adverse events are included in the secondary endpoint 4 analysis, as well as Pulse Generator-related and Non-Procedure Non-System-related adverse events that require invasive intervention to resolve.

If any of the following invasive interventions occur in order to resolve an above listed RV (separate from Plexa) lead-related, RA lead-related, LV lead-related AE, or an AE related to the Plexa lead and excluded from primary endpoint 1 and secondary endpoint 1 as listed in Section 9.3.1, the AE will be included in the secondary endpoint 4 analysis:

- Lead surgically repositioned
- Lead surgically explanted
- Lead surgically replaced
- Lead surgically abandoned
- Other lead-related surgery performed

Additionally, if any of the following non-invasive interventions occur in order to resolve an above listed RV (separate from Plexa) lead-related, RA lead-related, LV lead-related AE, or an AE related to the Plexa lead and excluded from primary endpoint 1 and secondary endpoint 1 as listed in Section 9.3.1, the AE will be included in the secondary endpoint 4 analysis:

- Lead pacing polarity or pacing mode reprogrammed in response to a problem with the mechanical or electrical integrity of the lead
- Lead programmed off in response to a problem with the mechanical or electrical integrity of the lead
- Lead use continued based on medical judgment despite a known clinical performance issue

AEs that are corrected by reprogramming the pulse generator (other than the above) and resolved without invasive intervention will not be considered an adverse event. For example, electrical reprogramming of the pacing polarity to eliminate extracardiac stimulation will not be considered an adverse event if not in response to a problem with the mechanical or electrical integrity of the lead. Similarly, increasing pacing output as a result of an elevated threshold without further intervention will not be considered an adverse event.

9.3.3 Serious Adverse Events

All adverse events included in the primary and secondary endpoint analysis are adjudicated by the CEC for seriousness. Adverse events are classified as serious if one or more of the following occurs:

- death
- serious deterioration in the health of the subject, that resulted in one of the following:
  - life threatening illness or injury
  - permanent impairment of a body structure or body function
  - in-patient or prolonged hospitalization
  - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or body function
- congenital anomaly / birth defect

Note: planned hospitalization or a pre-existing condition or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event. 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.

9.4 ADVERSE EVENT REPORTING

The adverse events that an IRB considers reportable are dependent on the particular IRB. To avoid underreporting, BIOTRONIK recommends that, at a minimum, the investigator reports the Plexa lead-related adverse events that occur during the Plexa Registry to BIOTRONIK and the IRB.

The registry site will report the adverse event on the Adverse Event eCRF. Additionally, registry sites may report adverse events through MedWatch, FDA's adverse event reporting tool for market-released devices. As defined in BIOTRONIK's internal procedures, these adverse events may be reported by BIOTRONIK through manufacturer's MedWatch reports.

10. OTHER GENERAL INFORMATION

10.1 PROTOCOL COMPLIANCE

The investigator is responsible for conducting the registry in accordance with the signed agreement, the protocol, applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB. The investigator shall notify BIOTRONIK and the reviewing IRB in writing no later than 5 working days after any significant deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Except in such emergency, prior approval by BIOTRONIK is required for significant deviations from the investigational plan.

BIOTRONIK categorizes protocol noncompliance instances as either violations or deviations. Both protocol violations and deviations will be reported during interim reports and the final report.

10.1.1 Protocol Violations

Protocol violations are defined as instances where the protocol requirements and / or regulatory guidelines were not followed, and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the plan and / or the rights, safety, or welfare of subjects. Protocol violations include, but are not limited to:

- Failure to obtain consent
- Subject inclusion / exclusion violations and protocol requirement violations that affect the primary endpoint of the registry design

These violations will be reported and the site must notify the reviewing IRB per the IRB's reporting requirements. The site should provide a copy of the IRB protocol noncompliance notification (as applicable) to BIOTRONIK. Protocol violations must also be reported to BIOTRONIK via Protocol Noncompliance eCRFs.

10.1.2 Protocol Deviations

Protocol deviations are deviations from the requirements of the protocol in such a manner whereby data is unusable or not available. Protocol deviations are less serious in nature and do not require IRB notification as long as they do not have an effect on the rights, safety, or welfare of the registry subject. Protocol deviations include, but are not limited to:

- Procedure not performed within the allowed timeframe
- Required data not obtained

The site must report protocol deviations to BIOTRONIK via Protocol Noncompliance eCRFs. Both protocol deviations and violations will be reported in progress reports.

10.2 STUDY TERMINATIONS

Once a subject is enrolled, every effort should be made to continue to follow the subject in the registry. However, it is inevitable that some subjects will decline to participate further, change geographic location, or become non-compliant with the visit schedule.

10.2.1 Withdrawal of Consent

If consent is withdrawn, obtain the date of withdrawal and reason for withdrawal of consent, then complete a Study Termination eCRF.

10.2.2 Subject Death

In the event of subject death during registry participation, personnel at the study site are asked to notify BIOTRONIK as soon as possible by completing a Study Termination eCRF. If subject death was associated with an adverse event, an Adverse Event eCRF will also be required.

The following information should be reported for any subject death:

- Death certificate, death report signed by the investigator, or relevant medical records that includes:
  - Date and time of death
  - Place death occurred
  - Identification of the rhythm at the time of death, if known (include any available documentation)
  - Immediate cause of death
  - Any other circumstances surrounding the death
- Whether death was related to Plexa lead
- Plexa lead return status

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

10.2.3 Plexa Lead or Pulse Generator Extraction

Any subject who has the Plexa lead explanted or capped, and is not re-implanted or will not be re-implanted with another Plexa lead attached to a US market released BIOTRONIK pulse generator, will be withdrawn from the registry. Additionally, any subject who has their BIOTRONIK pulse generator explanted and is not re-implanted with a US market released BIOTRONIK pulse generator will also be withdrawn from the registry (even if the Plexa lead remains). Only complete a Study Termination eCRF after documentation of the system revision procedure (see Section 3.2.5) is available. For example, if the Plexa lead and pulse generator are explanted due to infection, the subject should not be exited until a non-registry lead / system is implanted or documentation is available stating that the subject will not be re-implanted with a registry qualifying lead / system. Report the exit on the Study Termination eCRF and any adverse events resulting from the system revision.

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

10.2.4 Lost to Follow-up

Subjects lost to follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. Registry sites should attempt to contact these subjects in order to maintain registry visit compliance and all contact attempts should be documented. At a minimum, the site should make and document 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 should be exited from the registry by completing a Study Termination eCRF.

10.2.5 Registry Participation Complete

All subjects are expected to be followed for 5 years with a final visit interval at 60 months (± 45 days). After a subject completes their final routine visit in this time interval, their study participation is complete and the subject should be exited from the registry by completing a Study Termination eCRF.

10.3 INFORMED CONSENT

Prior to the subject's participation in the investigation, informed consent is required from all subjects. The investigator is required to inform BIOTRONIK and the reviewing IRB within 5 days if any subject was not appropriately consented to participate in the registry. In order to assist with the consent process, BIOTRONIK will provide a template subject consent form to sites participating in the registry.

10.4 IRB APPROVAL

IRB approval is required from each institution prior to participation in this registry. Subject enrollment may not begin until the IRB and BIOTRONIK have granted approval for the study site. IRB approval is also required throughout the duration of this clinical investigation. If IRB approval is withdrawn, BIOTRONIK must be notified within 5 working days.

10.5 OTHER INSTITUTIONS AND PHYSICIANS

This registry is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK and the appropriate IRB. Additional study sites may be included in this study. Only approved investigators are authorized to participate in the study. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in this registry (e.g. when a subject goes to the emergency room for medical treatment). In these instances a protocol deviation will not be issued and all available data will be utilized. In any such situations, the IRB and the investigator must continue to provide oversight for that subject's medical care and rights as a research subject.

11. RECORDS AND REPORTS

11.1 INVESTIGATOR RECORDS

Investigators are required to maintain on file the following accurate, complete and current records relating to this investigation:

- All correspondence relating to the registry with another investigator, an IRB, BIOTRONIK, a monitor, or the FDA, or any other regulatory authority (e.g., a letter sent from the investigator to the IRB).
- A copy of the Plexa Registry protocol
- Signed investigator or research agreement
- Signed Financial Disclosure Form
- A copy of the IRB letter approving the research registry
- A copy of the IRB approved subject Informed Consent Form
- All clinical forms and documentation, including:
  - A copy of the signed subject Informed Consent Form
  - All supporting documentation for data entered into the EDC system
  - Records of any adverse events, including supporting documentation
  - Records pertaining to subject deaths during the investigation
  - Documentation and rationale for any deviations from the clinical protocol
  - Any other records required by BIOTRONIK

11.2 INVESTIGATOR REPORTS

Investigators are required to prepare and submit to BIOTRONIK the following complete, accurate, and timely reports on this investigation when necessary:

- Notification of a subject death during the registry
- Notification of the withdrawal of IRB approval
- Annual progress reports prepared for the IRB
- Notification of any deviations from the registry plan
- Notification that an informed consent was not obtained from the subject
- Final summary report prepared for the IRB
- Any other information upon the request of an IRB, the FDA, or BIOTRONIK

Table 6 outlines the responsibilities, including time constraints, for submitting the above reports.

Table 6: Investigator Reporting Responsibilities

Type of Report	Report to BIOTRONIK	Report to IRB	Time Constraints of Notification
Subject Death During Registry	Required	Required	BIOTRONIK as soon as possible and as required by reviewing IRB
Adverse Event	Required	IRB dependent	Within 10 calendar days after notification of the event
Subject Withdrawal	Required	Required	BIOTRONIK as soon as possible and as required by reviewing IRB.
Withdrawal of IRB Approval	Required	N/A	Within 5 working days
Progress Report	Required	Required	Submitted not less often than yearly
Significant Deviations from Registry Plan	Required	Required	Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by BIOTRONIK is required
Informed Consent Not Obtained	Required	Required	As soon as possible after discovery and no more than 5 working days

11.3 SPONSOR RECORDS

BIOTRONIK will maintain the following records:

- All correspondence that pertains to the registry with the investigator(s), IRB, and the FDA
- Investigator agreements, financial disclosures, and curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events and complaints
- Adverse device effects
- Electronic case report form data
- Clinical investigation plan and report of prior investigations
- Monitoring reports
- Clinical progress reports

11.4 SPONSOR REPORTS

Table 7 outlines the responsibilities, including time constraints, for sponsor reports.

Table 7: Sponsor Reporting Responsibilities

Type of Report	Prepared by BIOTRONIK for	Time Constraints of Notification
Withdrawal of IRB Approval	Reviewing IRBs and participating investigators	Within 5 working days of receipt of notice of withdrawal of approval
Progress Report	All reviewing IRBs	A progress report will be submitted at least annually
Recall and Disposition	All reviewing IRBs	Notification will be made within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	All reviewing IRBs and participating investigators	A final report will be submitted within 6 months after completion or termination of the registry.

APPENDIX A: DEFINITION OF TERMS

Abnormal defibrillation impedance – Defibrillation impedance is typically considered abnormal if a measurement is < 25 Ω or > 150 Ω (based on lead model and measurement range of the device). Includes high or low shock impedance when attempting to deliver a shock.

Abnormal pacing impedance – Pacing impedance is typically considered abnormal if a measurement is <200 Ω or >3000 Ω (based on lead model and measurement range of the device).

ACC / AHA – American College of Cardiology / American Heart Association

AE (Adverse Event) – An unwanted affect detected in participants either implant procedure related, lead related, or other. The term is used whether or not the effect can be attributed to the leads in the study. For the purposes of this study, the CEC will indicate whether the adverse event's relation to the Plexa lead is: related, possibly related, not related, or unknown.

Cardiac perforation associated with a lead – Penetration of the lead tip through the myocardium (including microperforation), clinically suspected and confirmed by chest X-ray, fluoroscopy, echocardiogram, intracardiac electrogram, or visual observation.

CFR – Code of Federal Regulations

Chronic threshold – Chronic threshold is defined as the pacing threshold determined at the subject's 3 month follow-up visit. If a 3 month follow-up visit is not completed, the chronic threshold is considered the first available threshold after the 3 month follow-up interval.

Clinical failure – Inability of the lead to correctly sense or pace in the heart, not attributable to a physiologic reason (e.g. new onset atrial fibrillation) or a mechanical malfunction of the lead or pulse generator that remains unresolved despite reprogramming and / or repositioning.

DF-1 – the international standard whereby leads and generators from different manufacturers are assured a basic fit [Reference ISO 5841-3:2013]

DF4 – the international standard for defibrillation lead connectors [Reference ISO 27186:2010]

Exit block – The failure of an intact pacing system to capture the heart because the stimulation threshold exceeds the output of the pacemaker.

Explantation – Surgical removal of a lead during the acute implant stage, whereby the lead has not been chronically implanted and can be easily removed by simple traction.

Extracardiac stimulation – Clinical observation of inadvertent nerve / muscle stimulation other than cardiac muscle, such as the diaphragm or pectoral muscles..

Extraction of a lead – Surgical removal of a chronically implanted lead.

Failure to capture or intermittent capture – Intermittent or complete failure to achieve cardiac stimulation at programmed output delivered outside of the cardiac refractory period. This will be considered an AE if invasive intervention is taken. In the absence of invasive intervention, this will only be considered an AE if there is failure to capture the permanently programmed output with a minimum 2:1 safety margin. Sudden and significant increase in the pacing threshold value (elevated threshold compared to previous measured value) at which 2:1 safety margin can no longer be achieved.

Failure to sense or undersensing – Intermittent or complete loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings. This will be considered and AE if invasive intervention is taken. In the absence of invasive intervention, this will only be considered an AE if the loss of sensing is not due to a medical reason and cannot be resolved with reprogramming.

Hematoma – A localized collection of extravasated blood, usually clotted, in an organ, space, or tissue. A hematoma is not considered a protocol defined AE unless it is a major hematoma related to the implant procedure. See major hematoma.

High pacing threshold – High lead pacing threshold resulting in invasive intervention. In absence of invasive intervention, at follow-up, lead threshold that has increased two fold from the chronic threshold value, and is unable to achieve a 2:1 safety margin.

IS-1 – the international standard whereby leads and generators from different manufacturers are assured a basic fit [Reference ISO 5841-3:2013]

Lead conductor fracture – A mechanical break within the lead conductor (includes connectors, coils and / or electrodes) observed visually, electrically, or radiographically.

Lead dislodgment – Radiographic, electrical, or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing, and / or lead performance.

Lead insulation breach or insulation break – A disruption or break in lead insulation observed visually, electrically, or radiographically.

Loose set screw – Header set screw not properly tightened prior to end of implant or revision procedure.

LV lead – Left ventricular lead

Major hematoma – Hematoma requiring evacuation, drainage, blood transfusion, hospitalization, or extension of hospital stay to treat hematoma

Mechanical failure – Malfunction of the lead through a break in the conductor, insulation, or connector pin leading to loss of pacing / sensing observed visually, electrically, or radiographically. Confirmed or suspected mechanical failures induced by intervention, such as lead damage caused during a procedure, are not protocol defined adverse events.

Non-healing pocket dehiscence – Separation of wound edges around the pocket of the implanted pulse generator that has not healed.

Oversensing – Misinterpretation of cardiac or non-cardiac events as cardiac depolarization, such as T-waves, skeletal muscle potentials, and extracardiac electromagnetic interference (EMI).

Pneumothorax – Air or fluid in the pleural space surrounding the lung leading to collapse or partial collapse of the lung.

Premature battery depletion – Reaching Elective Replacement Indicator (ERI) before reaching 75% of the predicted date.

Pulmonary embolism – Blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream.

Pulse Generator Failure – Confirmed or suspected pulse generator issue that is due to a mechanical failure or electrical malfunction, such as inability to communicate with pulse generator, electrical circuit failure, or inability to deliver therapy, that is not attributable to another component of the system or caused by an external source.

RA lead – Right atrial lead

Skin erosion – Deterioration of tissue over an implanted device or the movement of a lead through the skin.

Suspected lead failure – Lead issue that is potentially a mechanical or electrical malfunction.

Tamponade – Compression of the heart caused by blood accumulation in the space between the myocardium and the pericardium.

Thrombosis – The development of a blood clot in a vein or artery that leads to the obstruction of blood flow.

Twiddler's syndrome – A condition where the pulse generator leads are dislodged by the subject unwittingly rotating the subcutaneous pulse generator.

Venous occlusion – Blockage of a vein causing a reduction of blood supply and associated symptoms.

REFERENCES

[1] Peto R, et al. Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of Each Patient. II. Analysis and Examples. *Br J Cancer* 1977;35:1-39
[2] Slotwiner D, et al. HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. *Heart Rhythm* 2015;12:e69-100