Clinical Protocol
for the
Protego DF4
Post Approval Registry

PROTEGO
Post-Approval Registry

NCT02243696

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Protego DF4 Post Approval Registry

PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the Protego DF4 Post Approval 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 U.S. federal regulations, ICH and GCP guidelines.

PRINCIPAL INVESTIGATOR:

Signed: _____

Name (please print)

_____ _____

Signature Date

SUMMARY

Title:	Protego DF4 Post-Approval Registry
Design:	Prospective, single-arm, non-randomized, multi-center registry
Purpose:	To confirm long-term safety and reliability of BIOTRONIK's Protego DF4 lead, as used in conjunction with a BIOTRONIK DF4 compatible implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) pulse generator. The evaluation of safety will be based on the analysis of Protego lead related adverse events. The Protego DF4 registry will provide data to permit characterization of any Protego lead failures contributing to loss of bradycardia or shock therapy. Additionally, acute and chronic Protego 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 BIOTRONIK Ilesto DF4 ICD or CRT-D or future market released BIOTRONIK DF4 ICD or CRT-D. Enrollment can be up to 30 days prior to or 30 days after implant with the DF4 system.
Enrollment:	This registry will include 1,694 subjects implanted with the Protego DF4 system. The collection of data will continue for 5 years post-implant for each enrolled subject.
Clinical Sites:	Up to 75 U.S. and International sites.
Primary Endpoints:	1. Evaluation of the overall incidence of adverse events (AEs) related to the Protego lead or device header 2. Evaluation of the incidence of each individual type of AE that contributes to Primary Endpoint 1
Secondary Endpoint:	1. Pacing threshold, sensing and impedance measurements for the Protego lead through 5 years post-implant 2. Shock impedance for the Protego lead through 5 years post-implant 3. AE rates for AEs excluded from primary safety endpoints 1 and 2, through 5 years post-implant
Clinical Events Committee Chair:	TBD
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 FDA post-approval registry for BIOTRONIK's Protego DF4 implantable cardioverter defibrillator (ICD) lead, further referred to as the Protego lead throughout this document. Currently this includes the following models: Protego SD (active fixation, dual coil), Protego TD (passive fixation, dual coil), Protego S (active fixation, single coil), and Protego T (passive fixation, single coil). Under this protocol, the Protego lead is utilized in conjunction with any market-released BIOTRONIK Ilesto or future US market released ICD or cardiac resynchronization therapy defibrillator (CRT-D) device with a DF4 header.

1.2 REGISTRY OVERVIEW

The purpose of this post-approval registry is to confirm the safety and reliability of the Protego lead as used in conjunction with any compatible BIOTRONIK Ilesto or future US market released DF4 ICD or CRT-D device. Data will be collected from up to 1694 subjects from implant through 5 years of follow-up.

Subjects eligible for the registry include those that will be implanted with a Protego lead within the 30 days following enrollment procedures or have been implanted with a Protego lead within 30 days of enrollment. Prior to enrollment procedures, subjects will be screened to ensure eligibility and will sign an informed consent. Consent and enrollment must occur at a maximum of 30 days prior to or post implant of the Protego lead.

Safety will be evaluated based on the analysis of all Protego lead and device header-related adverse events. Acute and chronic lead parameters for sensing, pacing thresholds, and pacing and shock impedance will be evaluated for the Protego lead. Additionally, acute and chronic lead parameters for sensing, pacing thresholds, and pacing impedance will be evaluated for all BIOTRONIK leads, including right atrial and left ventricular leads.

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

1.3 BACKGROUND

The Protego DF4 Post-Approval Registry is designed to document the clinical experience of the Protego leads as required by the FDA through P980023/S057, dated July 3, 2014.

The term DF4 refers to an industry standard header/lead connection scheme between an ICD/CRT-D device and the ICD lead. The DF4 header/lead system features a single connection between the ICD/CRT-D device and the ICD lead. As a result, the number of connectors for an ICD lead is reduced with a DF4 header/lead system compared to a

DF-1/IS-1 system, which simplifies the implantation procedure, reduces the likelihood of lead-to-port mismatch, and decreases the number of setscrews necessary to secure the lead into the header. Section 1.4.2 provides further details on differences between the DF4 and DF-1/IS-1 connection schemes. Additionally, by eliminating the lead yoke, the system pocket bulk can be reduced.

The Protego lead is a 7.8 French transvenous ICD lead designed for permanent right ventricular pacing, sensing, and delivery of defibrillation/cardioversion shocks to the heart. Protego is the successor of the Linox^{smart} ICD lead (Linox^{smart} SD/TD P980023/S038, approved September 17, 2010, Linox^{smart} S/T P980023/S043, approved February 28, 2011), the only major difference being the replacement of the traditional DF-1/IS-1 connectors of the Linox^{smart} lead with the DF4 connector. The Linox lead family has been extensively studied in the ongoing GALAXY registry.

1.3.1 GALAXY Lead Registry: Clinical Experience with Linox ICD Lead

BIOTRONIK is currently conducting GALAXY, 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. There were 1999 subjects enrolled in the registry, 196 of which were implanted with Linox^{smart} leads.

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 Linox and Linox^{smart} lead models was 0.63 ± 0.33 V. The mean sensing amplitude was 12.83 ± 5.43 mV. The mean lead impedance was 556.7 ± 124.8 ohms. There were 5 (2.55%) subjects who experienced a primary adverse event (AE) reported as related to the Linox^{smart} lead (Table 1) and 29 (1.45%) subjects who experienced a primary AE related to the Linox Lead Family.

Table 1: Linox Smart Lead Related Adverse Events

Adverse Event	Linox^{smart} Leads (n=196)			All Linox Lead Models (N=1,999)		
	Subjects with AE, n	% Subjects with AEs	AEs, n	Subjects with AE, n	% Subjects with AEs	AEs, n
Primary Endpoint AEs						
Other ICD lead related: Lead oversensing or noise	3	1.53%	3	13	0.65%	13
Lead dislodgement > 180 days	1	0.51%	1	5	0.25%	5
Lead impedance out of range, High impedance, Potential conductor fracture	1	0.51%	1	5	0.25%	5
Lead impedance out of range, Low impedance, Potential insulation break	0	0.00%	0	5	0.25%	5
Lead undersensing or loss of sensing	0	0.00%	0	2	0.10%	2
Other ICD lead related: Tension pneumothorax	0	0.00%	0	1	0.05%	1
Total Primary Endpoint AEs	5	2.55%	5	29	1.45%	31
Secondary Endpoint AEs Related to the ICD Lead						
Lead dislodgement < 180 days	2	1.02%	2	22	1.10%	22
High pacing threshold, intermittent capture, no lead capture	0	0.00%	0	7	0.35%	7
Cardiac perforation with or without tamponade	0	0.00%	0	4	0.20%	5
Total Secondary Endpoint AEs	2	1.02%	2	33	1.65%	34
Total Primary or Secondary AEs	7	3.57%	7	60	3.00%	65

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 4, 2013, is assumed for all active subjects.

The standard error (SE) for the estimated survival (freedom from AEs) was calculated using the method of Peto et al. The last adverse event occurred on day 1,465, and the current estimated freedom from adverse events is 97.5% (SE 1.0%) for implant times 1,465 days or longer. These estimates may change as additional follow-up data are collected.

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

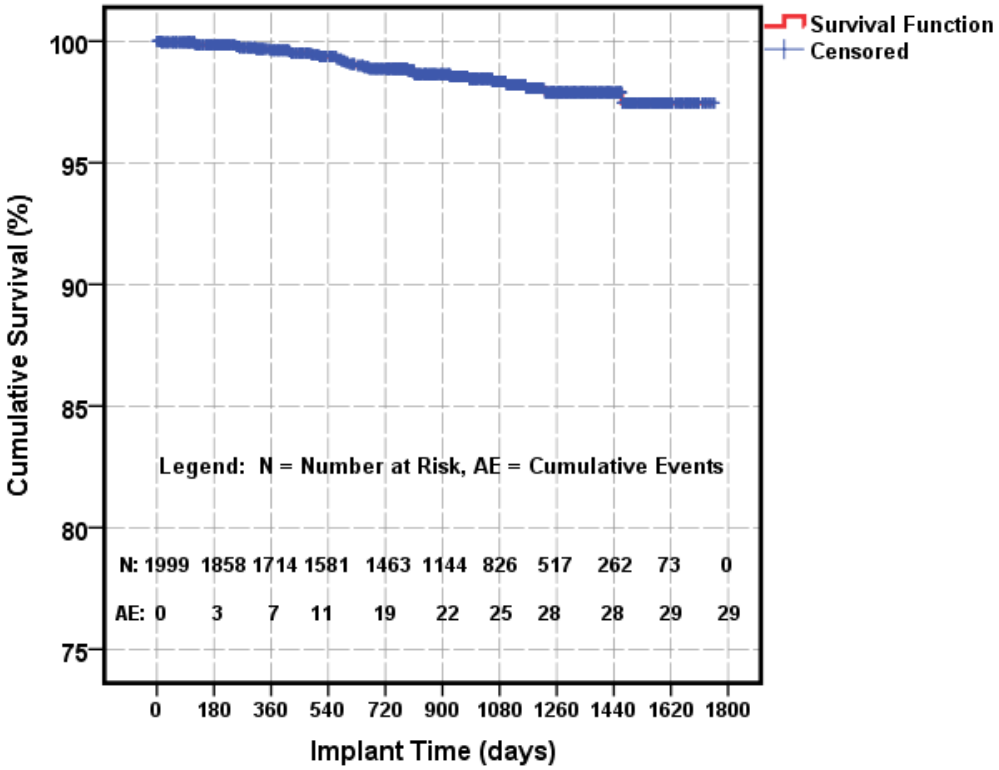


Table 2: Primary Endpoint Case Summary

Total Subjects, n	Subjects with Adverse Event, n	Censored	
		n	%
1999	29	1970	98.5%

1.3.2 Protego Animal Study

The safety and efficacy of the BIOTRONIK Linox^{smart} DF4 SD lead along with the Iforia or Ilesto 7 DF4 ICD (equivalent devices) were evaluated by comparison to the FDA-approved BIOTRONIK Linox^{smart} SD lead. The Protego family of ICD leads was developed and tested with the engineering project name "Linox^{smart} DF4". Therefore, all references to this device name are synonymous with the Protego family of ICD leads.

The animal study began May 30, 2013, was randomized, and compared the two ICD systems implanted in a total of 24 healthy canine subjects (N=12/group) over a period of 12 weeks. Ventricular pacing capture threshold (PCT), painless shock impedance (PSI), serious adverse device event -free rate (SADE-free), R-wave amplitude, and ventricular pacing impedance (VPI) of the ICD systems implanted for 12 weeks were the focus of primary and secondary endpoints.

All primary endpoints were achieved, as the DF4 system demonstrated non-inferiority of PCT and equivalence of PSI in all three shock pathways relative to the DF-1 system, along with a 100% SADE-free rate. In addition, all secondary endpoints were achieved,

as the DF4 system demonstrated non-inferiority of R-wave amplitude and equivalence of VPI relative to the DF-1 system. The results of this study demonstrate that the BIOTRONIK Iforia/Ilesto DF4 ICD equipped with the Linox^{smart} DF4 SD lead is comparable in terms of efficacy and safety to its predecessor, the BIOTRONIK Iforia/Ilesto DF-1/IS-1 ICD equipped with the Linox^{smart} SD lead.

1.4 DEVICE DESCRIPTION

1.4.1 Protego Lead Description

The Protego ICD lead is a 7.8 F transvenous, steroid-eluting, endocardial lead for use with any ICD/CRT-D with a DF4 connector port (Figure 2). Protego leads are variants of currently marketed Linox^{smart} ICD leads with IS-1 and DF-1 connectors. The functionality of each lead is identical to the respective predecessor Linox^{smart} ICD lead.

The Protego S and Protego T leads have two sensing and pacing electrodes (distal tip and ventricular ring electrode) and one defibrillation electrode (ventricular shock coil). The Protego SD and Protego TD 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 device;
- conduct bradycardia and anti-tachycardia pacing pulses emitted from the device to cardiac tissue;
- conduct defibrillation shocks of both high and low energies from the device to cardiac tissue.

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

The Protego S and Protego SD 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 Protego T and Protego TD leads feature a passive fixation tip coated with fractal iridium.

The distal tip of all Protego ICD 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.

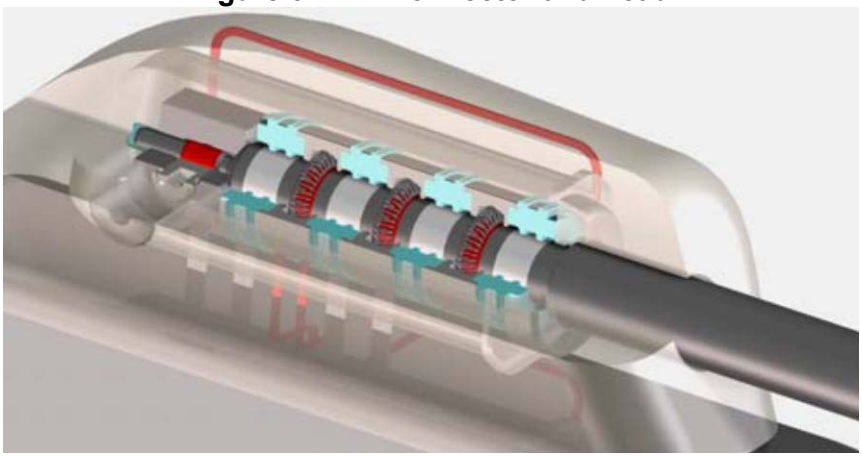
The DF4 connector of Protego ICD leads was designed in compliance with ISO 27186; the specifications such as geometry, tensile loads, etc., of the DF4 connector meet the requirements of this standard. The DF4 connector allows use with ICDs/CRT-Ds that have connector ports conforming to ISO 27186.

Figure 2: Protego Lead

1.4.2 Design Differences between Protego and Linox^{smart}

Differences between the currently approved Linox^{smart} leads and the Protego leads are limited to the replacement of DF-1 and IS-1 connectors with a DF4 connector and a modified transition area between connector and lead body (Figure 3). The electrical components of Protego leads located from lead body to the lead tip remain unchanged compared to Linox^{smart} leads.

Figure 3: DF4 Connector and Lead



1.4.3 DF4 Device Header Description

The DF4 connector features a single connection between the ICD/CRT-D and the ICD lead. As a result, the number of connectors for ICD leads is reduced from two or three connectors for a single shock coil or a dual shock coil DF-1/IS-1 ICD lead (see Figure 4 and Figure 6), respectively, to a single connection with a DF4 ICD lead (see Figure 5 and Figure 7).

Figure 4: Linox^{smart} SD Schematic

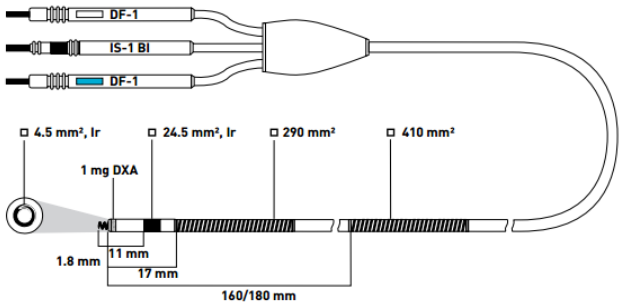


Figure 5: Protego SD Schematic

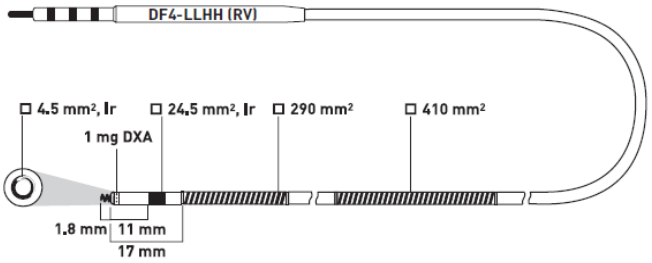


Figure 6: Orientation of DF-1/IS-1 Ilesto Headers

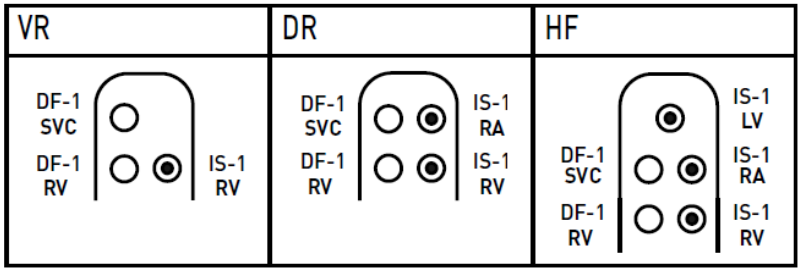
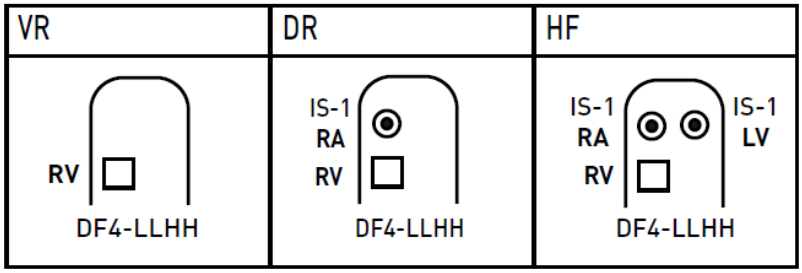


Figure 7: Orientation of DF4/IS-1 Ilesto Headers



VR – Single Chamber Device, DR – Dual Chamber Device, HF – Triple Chamber Device

Due to these modifications, DF4 systems require a more complex design of the generator connector cavity. Three of the four setscrews that are necessary for a dual coil DF-1/IS-1 shock lead have been replaced by spring contacts. Additionally, strict requirements are put on the seals that have to prevent leaking current as well as prevent liquid from entering the header cavity. Conformity with this standard ensures that the DF4 generator connector can be connected to any DF4-labelled lead. For purposes of the Protego DF4 post-approval registry, the BIOTRONIK Protego ICD lead is required.

1.4.4 BIOTRONIK Home Monitoring®

Current expert consensus advocates 3- to 6-month device evaluations either in-person or by remote monitoring for ICD/CRT-D devices[1].

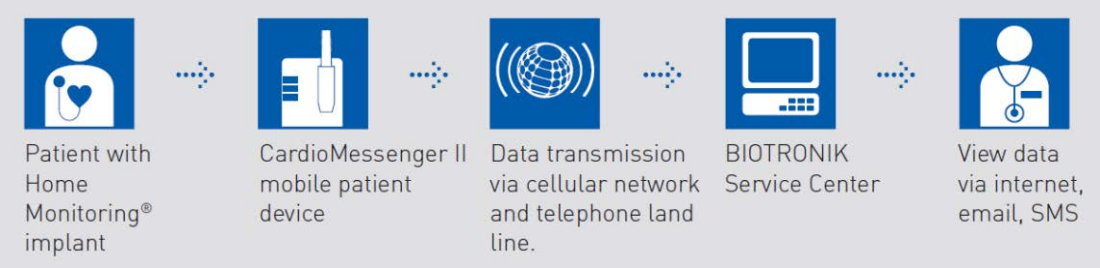
BIOTRONIK Home Monitoring® is a communication system which allows the automatic transmission of diagnostic patient data from the device to the physician at any time. The technology implements the use of wireless communications to provide the physician with daily patient monitoring and trend analysis information between office follow-up visits. A block diagram of the transmission path is shown in Figure 8, and the transmission steps are described as follows:

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

- 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.

- 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 8: Home Monitoring® Transmission Path



[1] Wilkoff BL, et al. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. *Heart Rhythm* 2008;5:907-25

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

- BIOTRONIK Home Monitoring® information may be used as a replacement for device interrogation during in-office follow-up visits.

- 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. Home Monitoring® data is helpful in determining the need for additional in-office follow-up.

- 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.

- BIOTRONIK Home Monitoring® provides early detection of arrhythmias.

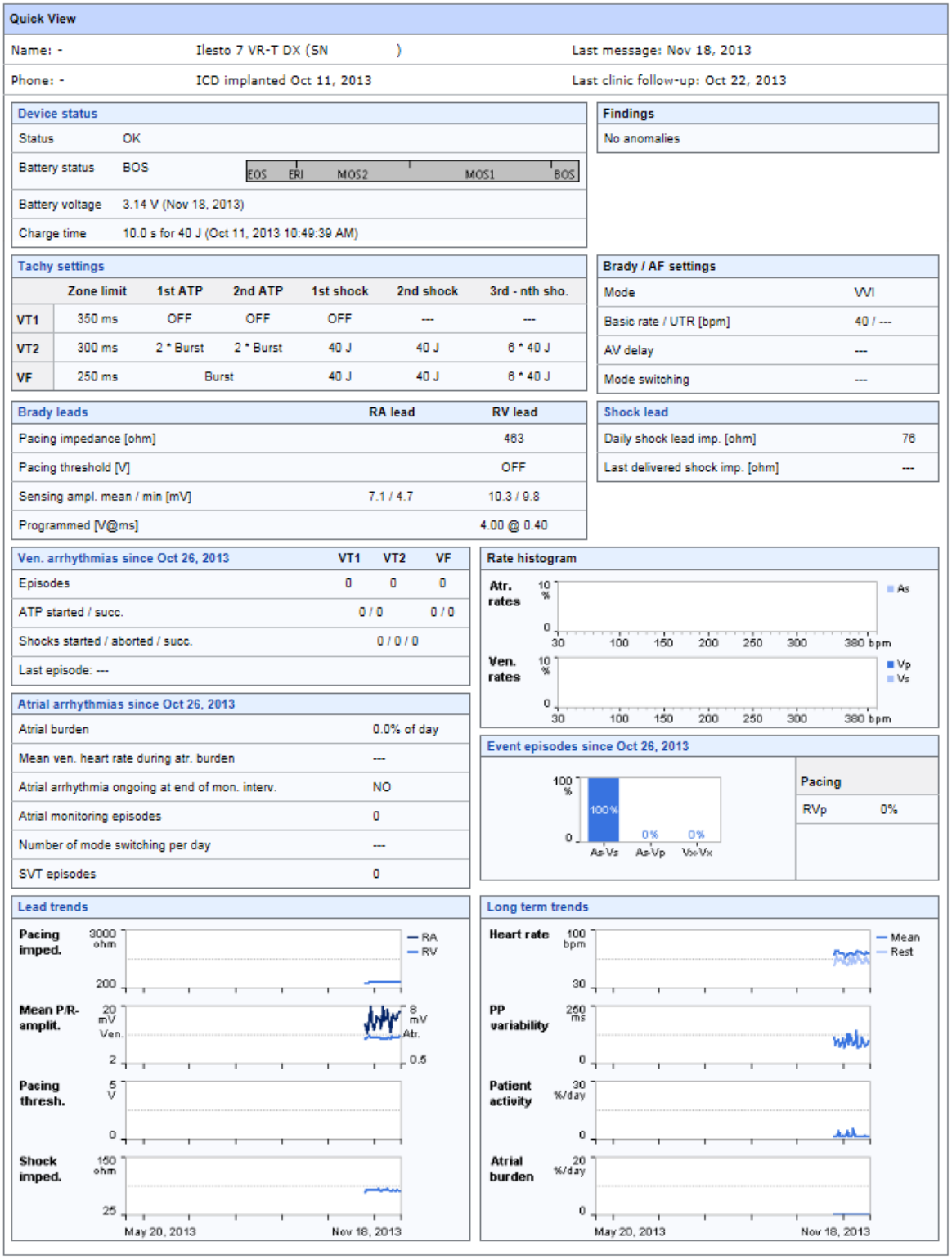
- BIOTRONIK Home Monitoring® provides early detection of silent, asymptomatic arrhythmias.

- Automatic early detection of arrhythmias and device system anomalies by BIOTRONIK Home Monitoring® allows for earlier intervention than conventional in-office follow-ups.

- 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 the Ilesto ICD and CRT-D devices, Home Monitoring® provides event and system information similar to what is currently available during office follow-up visits. The highlighted information in the Home Monitoring® Quick View Summary Report, Figure 9, displays the study related follow-up data automatically transmitted on a daily basis including: battery status, pacing impedance, pacing threshold, sensing amplitude (mean/min) for both the atrial and ventricular leads. In addition, Home Monitoring® provides automatic daily information on arrhythmias, lead trends, current device programming, event episodes, therapy provided, and long term data trends.

Figure 9: Home Monitoring® Quick View Summary Report



2. REGISTRY DESIGN

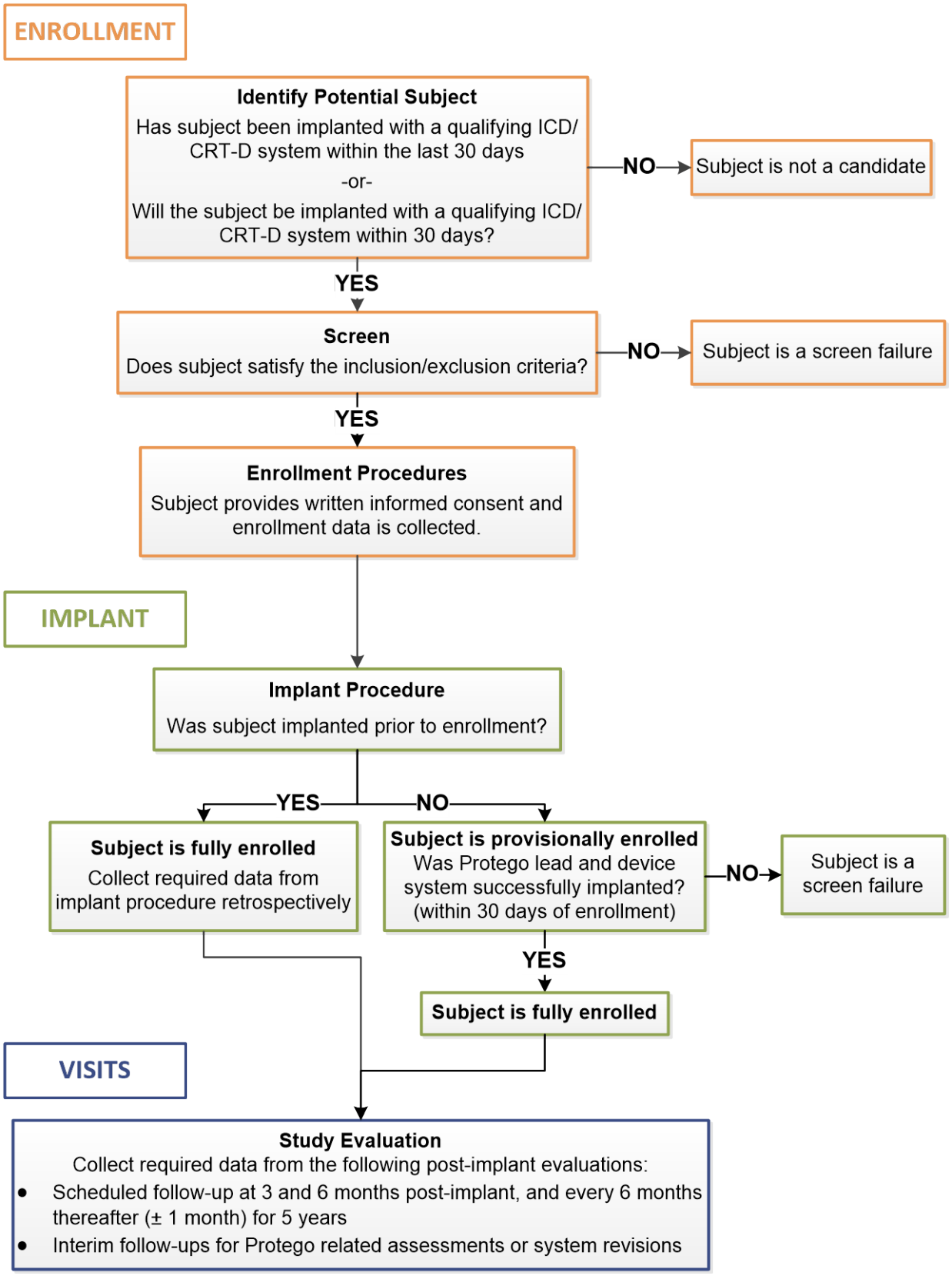
This multi-center, prospective, non-randomized registry is designed to gather safety data on BIOTRONIK's Protego leads. All subjects enrolled in the registry will be implanted with a US market released BIOTRONIK DF4 ICD or CRT-D pulse generator and a Protego lead.

Potential subjects will be identified by the investigator from their general patient population and must have an approved indication for receiving an ICD or CRT-D device. Additionally, potential subjects must satisfy the registry inclusion and exclusion criteria (Sections 3.1.3 and 3.1.4). If a patient has been determined to be eligible, informed consent is obtained prior to initiating any registry related procedures. After written informed consent has been obtained, enrollment visit data will be collected. Written informed consent and enrollment visit data collection may be obtained ± 30 days from the date of implant. If consent is obtained and eligibility is determined prior to implant, patients are considered 'provisionally enrolled' until they are successfully implanted, at which time they are considered fully enrolled. Device data and any adverse events will be collected from the date the first implant attempt onwards. If a patient is enrolled post-implant, device data and any adverse events since the date of the first implant attempt will be collected retrospectively at the enrollment visit.

After enrollment, subjects will be seen for an evaluation at three and six months post implant, and every six months thereafter for five years. Subjects with Home Monitoring® capabilities will be seen for an in-office follow-up at least once every 12 months and have the option to substitute a Home Monitoring® follow-up for every other in-office follow-up to result in the six month follow-up schedule. Registry visits completed using Home Monitoring® data will be accompanied by a phone call to the subject for a short verbal assessment. Subjects without a Home Monitoring® system will be seen for an in-office follow-up at three and six months post implant, and at least once every six months thereafter.

Figure 10 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 5.

Figure 10. Study Design Flowchart



2.1 REGISTRY ENDPOINTS

This registry includes the assessments of two primary safety endpoints related to the Protego DF4 lead, and several secondary endpoints that evaluate the safety and effectiveness of the BIOTRONIK ICD/CRT-D system with a Protego DF4 lead.

2.1.1 Primary Endpoint 1: Protego DF4 Lead Safety – 5-Year Adverse Event-Free Rate

The purpose of primary endpoint 1 is to evaluate the overall incidence of adverse events related to the Protego DF4 lead or header (as defined in Section 10) from implant through 5 years. Assuming that the expected Protego DF4 lead or header-related 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 Protego DF4 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 Protego DF4 lead at 5 year post-implant is greater than 92.5%

$$AEFR > 92.5\%$$

A rejection of the null hypothesis would demonstrate that the adverse event-free rate is greater than 92.5%.

2.1.2 Primary Endpoint 2: Protego DF4 Lead Safety – Individual 5-Year Adverse Event-Free Rates

Each of the individual types of adverse events contributing to primary endpoint 1 will be evaluated separately in the following superiority hypothesis.

H_o: The individual adverse event rate (AEIndividual) for a given type of AE for the Protego DF4 lead at 5 years post-implant is greater than or equal to 1%

$$AEIndividual \geq 1\%$$

H_a: The individual adverse event rate (AEIndividual) for a given type of AE for the Protego DF4 lead at 5 years post-implant is less than 1%

$$AEIndividual < 1\%$$

If the two-sided, 95% upper confidence bound is no more than 1% for individual adverse events, then the null hypothesis will be rejected for that AE type.

2.1.3 Secondary Endpoints

There are no formal tests of hypotheses associated with secondary endpoints 1-3.

1. Pacing threshold, sensing and impedance measurements for the Protego DF4 lead through 5 years post-implant.
2. Shock impedance for the Protego lead through 5 years post-implant.
3. Adverse event rates for protocol defined, CEC adjudicated AEs excluded from primary safety endpoints 1 and 2, through 5 years post-implant.

2.1.4 Additional Data of Interest

Additional information will be collected to characterize the registry population, implanted system, and progress of the registry. The collected information will include baseline demographics, medical history, implanted system, system revisions, Protego extractions, returned product analysis, and compliance. Specifically, data of interest will include:

- Baseline demographics, including age, gender, weight, height, New York Heart Association (NYHA) class, ejection fraction, and race and ethnicity (optional)
- Medical history, including indication for device
- Implanted device data, including pulse generator and leads models, serial numbers, and implant dates from initial implant and/or revisions
- Implant procedure data (collected retrospectively if implant occurred prior to enrollment)
- Pacing threshold, sensing and impedance measurements for implanted BIOTRONIK RA and LV leads
- Site reported adverse events excluded from primary and secondary endpoint analysis
- Protego DF4 extraction experience
- Results from returned product analysis
- Compliance to protocol requirements and registry visit schedule

2.2 REGISTRY SIZE

To document the clinical experience of the Protego DF4 lead as required by the FDA, the Protego DF4 post-approval registry is designed to follow 1694 subjects for 5 years post-implant at up to 75 U.S. and International sites.

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

2.3 SAMPLE SIZE ANALYSIS

The estimated sample sizes required to evaluate primary endpoints 1 and 2 are based on a superiority comparison of the overall Protego DF4 lead AE free-rate to 92.5% at 5 years, and a non-powered, superiority comparison for those individual lead-related AEs to 1% at 5 years. The sample size for primary safety endpoint 1 was calculated based on the following assumptions:

Assumptions for primary safety endpoint 1

- Study 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 Protego Leads
- Performance goal for AE-Free Rate at 5 years: 92.5%

For primary safety endpoint 1, a total of 750 evaluable Protego leads would be required to demonstrate superiority to an AE free-rate of 92.5% (see Table 3). 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.

Assumptions for primary safety endpoint 2

- Estimated individual AE rate at 5 years: 0.4%
- Allowable two-sided, upper 95% confidence bound: 1%

For primary safety endpoint 2, a total of 1000 evaluable subjects with Protego DF4 leads would be required to demonstrate a two-sided, upper 95% confidence bound of 1%, assuming an expected individual AE rate of 0.4% (see Table 3). 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 1694 ($=1000/0.9^5$) subjects would be required for evaluation of primary safety endpoint 2.

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 loss to follow-up rate encompasses all causes for subjects to be exited from the registry, including death, device explants, subject directed withdrawals, physician-directed withdrawals, and loss of contact with the subject.

Table 3: Primary Safety Endpoints Sample Sizes

	Primary Safety Endpoint 1	Primary Safety Endpoint 2
Sample Size of Evaluable Subjects	750 subjects	1000 subjects
Total Adjusted for Attrition	1271 subjects	1694 subjects

2.4 DATA ANALYSES

The analysis population for all primary endpoints in the registry will be the intention-to-treat (ITT) population. This population analysis will include all subjects who provide informed consent, met the enrollment criteria, and in whom a Protego lead was successfully implanted. Subjects enrolled prior to the Protego lead implant but not successfully implanted due to a Protego lead related complication (such as cardiac perforation caused by the Protego lead) will also be included in the ITT population.

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

Confidence intervals for the AE free-rate will also be estimated based on Kaplan-Meier estimates for freedom from adverse events together with the associated standard errors.

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%. Equivalently, the two-sided 95% lower confidence bound for the absolute difference between the overall AE free-rate and 92.5% must exceed zero.

The evaluation of primary safety endpoint 2 will be based on the exact, two-sided 95% confidence interval for the observed, individual AE rates at 5 years. The upper bound of these 95% confidence intervals must be less than 1%.

Secondary endpoints 1 and 2, which summarize pacing thresholds, sensing, impedance measurements and shock impedance measurements for the Protego lead, will be reported via standard measures, including means, standard deviations, medians, minimums, and maximums.

Secondary endpoint 3, 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 endpoints are evaluated at 5 years post-implant against pre-specified performance levels (92.5% for overall freedom from Protego lead-rated AEs, 1% for individual AE rates). To monitor the ongoing incidence of any potential AEs against the accumulating follow-up exposure post-implant, Kaplan-Meier survival curves will be prepared at the reporting intervals for these safety outcomes. Root causes for any failures, regardless of the incidence rates, will be investigated.

If the observed cumulative survival rates fall below the 5-year target values (92.5% of overall freedom from AEs, 99% for individual AEs) at any time during the registry, or are projected to fall below the target values, then BIOTRONIK will summarize the observed data and the results of its failure investigations, and report the findings to the FDA at or before the next scheduled status report. If at any time a single unanticipated adverse event or device failure, or combination of events, is believed to have implications regarding the safety of current or future subjects, then this will be reported to the FDA within the statutory timeframes.

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 forms 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 will be documented. BIOTRONIK will examine both missing-data patterns, which describe which values are observed and which are missing, and the missing-data mechanisms, which concerns the relationship between missingness and the values of variables in the registry data set[2].

For evaluation of the long-term primary registry endpoints (safety endpoints 1 and 2), 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 endpoint of other AEs at 5 years, excluded from the primary safety analyses, will be analyzed in similar manner. There will be no imputation for these missing adverse event outcomes.

For purposes of Kaplan-Meier survival analyses, described in Section 2.4.2, all AE data on enrolled subjects will be included with follow-up times censored at the time of withdrawal or last completed follow-up visit representing the time of the last known AE status.

[2] R.J.A. Little and D.B. Rubin, 2002, Statistical Analysis with Missing Data, 2nd edition, Wiley and Sons

Secondary endpoints, which include successful sensing and pacing, pacing thresholds, sensing and impedance measurements will be analyzed in two ways. First, all available results will be summarized by scheduled visit through the 5 years of registry follow-up. Secondly, a last value carried forward (LVCF) will be used to estimate the values at the final 5-year follow-up evaluation for subjects who withdraw prior to 5 years.

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.

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 subjects and selecting those who are appropriate for registry inclusion. Those selected for participation should be from the investigator's general patient population according to the indications below. Additionally, potential subjects will be evaluated against the inclusion and exclusion criteria described in Sections 3.1.3 and 3.1.4.

3.1.1 Indications

The Protego lead is a 7.8 French (8 F introducer) transvenous, steroid-eluting, bipolar, DF4 compatible ICD lead intended for permanent implantation in the right ventricle to provide pacing/sensing in the right ventricle and defibrillation/cardioversion shocks to the heart. For this registry, the Protego lead is utilized in conjunction with any market-released BIOTRONIK Ilesto or future US market released ICD/CRT-D device with a DF4 header.

3.1.2 Contraindications

Transvenous endocardial leads are contraindicated in the presence of severe tricuspid valvular disease and in patients with a mechanical tricuspid valve. The Protego DF4 lead is additionally contraindicated for patients who cannot tolerate a single systemic dose of dexamethasone acetate (DXA) of up to 1.3 mg for active fixation leads or 1.0 mg for passive fixation leads.

3.1.3 Inclusion Criteria

To support the objectives of this investigation, patients are required to meet the following inclusion criteria prior to enrollment:

- Implanted within the last 30 days or candidate for implantation of a BIOTRONIK ICD or CRT-D DF4 compatible system along with the Protego DF4 lead
- Meets ICD or CRT-D system implant recommendations as defined in guidelines published by relevant professional societies
- Able to understand the nature of the registry and provide informed consent
- Available for follow-up visits on a regular basis at the investigational site for the expected 5 years of follow-up
- 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 patient enrollment include the following requirements:

- Enrolled in any investigational cardiac device trial
- 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
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Patients reporting pregnancy at the time of enrollment

3.2 REGISTRY PROCEDURES

Patients will be enrolled ± 30 days from implant of a BIOTRONIK DF4 compatible ICD or CRT-D device and Protego lead. BIOTRONIK Home Monitoring® should be activated in subjects who have a Home Monitoring® system. Home Monitoring® data can be utilized to assist in triage and diagnosis of lead-related adverse events between scheduled follow-ups. Subjects with a Home Monitoring® system will be seen for a routine in-office follow-up at least every 12 months and have the option to be followed by Home Monitoring® between routine in-office follow-ups at the intervening 6 month intervals. Subjects without a Home Monitoring® system will be seen for a routine in-office follow-up at least every 6 months.

Registry Procedure Visits:

- Enrollment
- Implant (collected retrospectively if before enrollment)
- Routine follow-up evaluations at 3 months post-implant and every 6 months post-implant for 5 years
- Interim evaluations for Protego lead-related events or system revisions

Table 4 summarizes the visit assessment schedule.

Table 4: Registry Visit Assessment Schedule

	Enrollment	Implant[1]	Routine Follow-up 3 Months and 6-60 Months (every 6 months ± 1 month)[2]	Interim Evaluation (if applicable)
Informed Consent (enrollment)	X			
Demographics and Medical History	X			
Collect Implant Information	X[3]	X[3]		X
Device Evaluation		X	X	X
Adverse Event Assessment		X	X	X
Complete eCRF	X	X	X	X

[1]Implant must be completed within 30 days of or no more than 30 days prior to enrollment/informed consent.
[2]Subjects using Home Monitoring® will be seen for a routine in-office follow-up at least every 12 months and may be followed by Home Monitoring® between routine in-office follow-ups at the intervening 6 month intervals. Subjects not using Home Monitoring® will be seen for a routine in-office follow-up at least every 6 months. If a registry visit is conducted via Home Monitoring® the site is required to call the subject on the date of the Home Monitoring® data collection and document the Investigators assessment of possible adverse events since the last registry visit.
[3]If implant was completed prior to enrollment, implant data is collected retrospectively at the enrollment visit. If the subject was enrolled prior to implant, implant data will be collected and entered at the time of the implant procedure.

3.2.1 Registry Pre-Screening

Prior to enrollment, the patient's medical history must be reviewed in order to ensure they are an appropriate candidate for the registry. In addition, all patients must satisfy the registry inclusion and exclusion criteria prior to enrollment, including being a candidate for or having been implanted with a BIOTRONIK Protego lead and DF4 compatible ICD or CRT-D within the last 30 days.

3.2.2 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 procedures. The consent process, including discussion of the registry, will be documented in the patient's medical record. A patient is considered enrolled in the registry upon signing the Informed Consent Form and undergoing an attempt to implant the Protego DF4 lead. If a patient is consented and undergoes enrollment procedures prior to implant, they are considered 'provisionally enrolled' until they are successfully implanted, at which time they are considered fully enrolled. The visit at which informed consent is obtained is the enrollment visit and occurs ± 30 days from the date of implant. If implant occurs prior to enrollment, the date of implant and system information must be available for the patient to be enrolled. Patient demographics are to be obtained at the enrollment visit; however,

height and weight may be historical if this information is not available, with proper source documentation.

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

- Obtain Informed Consent
- Collect subject demographics (gender, height, weight, etc.)
- Medical history of subject, including device implant indications
- Complete all required eCRFs

3.2.3 Protego Implant

Implant will be completed ± 30 days from the enrollment visit. Implant details and device data will be collected retrospectively if implant occurred prior to enrollment.

The following data collection and reporting procedures are performed at implant:

- Collect implant information
    - Date of implant
    - Implant approach/method, and venous access
    - Implant success
    - If DFT testing was completed during implant, shock energy and impedance used during test
- Collect information on implanted system (pulse generator and leads manufacturer/model, serial numbers, etc.).
- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width.
- Record any lead-related, pulse generator-related and procedure-related adverse events during implant and complete an Adverse Event eCRF. Protego lead related adverse events should be reported even if the implant attempt is unsuccessful.
- Program parameters to best suit the needs of the subject.
- Complete all required eCRFs.

Patients that are provisionally enrolled, but never successfully implanted with the Protego lead, will be considered screen failures. If they undergo an implant attempt, but are not successfully implanted due to a Protego lead related adverse event (such as

cardiac perforation caused by the Protego lead) they will also be included in the intention-to-treat (ITT) population.

3.2.4 Routine Follow-ups

Three and six months (± 30 days) after successful implant and every six months (± 30 days) thereafter, subjects will undergo an assessment of their implanted system. Subjects with Home Monitoring® capabilities will be seen for a routine in-office follow-up at least once every 12 months and have the option to substitute a Home Monitoring® evaluation for every other in-office follow-up to result in the six month follow-up schedule. Additionally, each Home Monitoring® follow-up will be accompanied by an assessment via telephone call within 7 days, documenting clinical signs and symptoms. Subjects not using Home Monitoring® will be seen for a routine in-office follow-up at least once every six months.

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

The following study procedures are performed at routine in-office follow-ups:

- Interrogate and print initial programmed parameters and view stored diagnostic data.
- Record and print electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width.
- Evaluate device diagnostics, electrical parameters and programmed parameters to ensure the device is correctly pacing, sensing, and providing appropriate therapy.
- Record and print cumulative episode counters.
- Determine if there have been any adverse events (as defined in Section 10). If any are recorded, complete an Adverse Event eCRF.
- Interrogate and print the final programmed parameters.
- Complete all appropriate eCRFs.

The following study procedures are performed for a Home Monitoring® evaluation:

- Collect programmed parameters and view stored diagnostic data.
- Record electrical parameters of the implanted leads.
- Evaluate device diagnostics, electrical parameters and programmed parameters to ensure the device is correctly pacing, sensing, and providing appropriate therapy.
- Record cumulative episode counters.

- Perform phone interview within 7 days of Home Monitoring® report.
- Determine if there have been any adverse events (as defined in Section 10). If any are recorded, complete an Adverse Event eCRF.
- Complete all appropriate eCRFs.

3.2.4.1 Device Programming

If Home Monitoring® evaluations will be used for routine follow-up visits, atrial and ventricular capture control should be programmed to “ON” or “ATM,” and Home Monitoring® activated. If atrial and ventricular capture control is not programmed “ON”/”ATM” or goes off automatically due to AF, high intrinsic rate, or other reason, the investigator will provide reasons in the EDC system.

3.2.5 Unscheduled Interim Follow-ups

Unscheduled interim follow-ups may occur anytime during the registry. Data collection is only required when a subject is seen for Protego lead-related reasons or due to a protocol defined adverse event. Other hospital or clinic visits that are unrelated to the device are not required to be entered into the EDC system.

3.2.5.1 Protego Related Interim Follow-ups

For unscheduled interim in-office follow-ups related to the Protego lead (but not including a system revision), the data collection and reporting requirements are the same as those required for routine follow-ups (Section 3.2.4).

3.2.5.2 System Revisions

For interim evaluations that involve a system revision (even if the Protego lead is not directly affected), the following are required:

- Collect implant information
  - Date of revision
  - Implant approach/method, and venous access
  - Implant location of pulse generator and implanted leads
- Record extraction experience (if applicable).
- Collect information on newly implanted system (pulse generator and leads manufacturer/model, serial numbers, etc.).
- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width.

- Record any lead-related, pulse generator-related and procedure-related adverse events during implant and complete the Adverse Event eCRF.

- Set programming parameters to best suit the needs of the subject.

- Complete System Revision and Out of Service (OOS) eCRF, as applicable.

If the Protego lead is replaced with another Protego lead, the subject will continue participation in the registry based on the original implant date and visit schedule. If the Protego lead is explanted and the subject does not receive a new Protego lead, the subject will be withdrawn from the registry. See Section 3.3.3 for details on withdrawals due to lead or pulse generator extraction.

3.3 REGISTRY EXITS

Once a subject is enrolled and successfully implanted, 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.

3.3.1 Withdrawal of Consent

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

3.3.2 Subject Death

In the event of subject death during registry participation, personnel at the investigational site are asked to notify BIOTRONIK as soon as possible by completing an Out of Service and Registry Exit 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 or death report, signed by the investigator, 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 device or procedure related

- Timing for Institutional Review Board (IRB) or Ethics Committee (EC) notification (if required by the IRB/EC)

- Protego lead return status

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

3.3.3 Protego Lead or Pulse Generator Extraction

Any subject who has the Protego lead explanted or capped, and is not implanted with another Protego lead, will be withdrawn from the registry. Additionally, any subject who has their BIOTRONIK pulse generator explanted and replaced with a non-BIOTRONIK device will also be withdrawn from the registry (even if the Protego lead remains). Only complete a registry exit eCRF after documentation of the system revision procedure (see Section 3.2.5.2) is available. For example, if the Protego 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 Registry Exit eCRF and any adverse events resulting from the explant procedure.

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

3.3.4 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 Registry Exit eCRF.

3.3.5 Registry Participation Complete

All subjects are expected to be followed for a minimum of 59 months accounting for the visit expectation of 60 months (5 years) ± 1 month. 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 Registry Exit eCRF.

4. REGISTRY ORGANIZATION

4.1 SPONSOR

BIOTRONIK is the sponsor of the Protego DF4 post-approval registry. A sponsor is defined as an entity that initiates but does not conduct an investigation. BIOTRONIK's responsibility as the clinical registry sponsor is to ensure protocol and regulatory compliance through proper monitoring of the investigation. BIOTRONIK is required to ensure that the registry device is used under the immediate direction of an investigator.

4.2 CLINICAL EVENTS COMMITTEE

A Clinical Events Committee (CEC) consisting of at least 3 independent electrophysiologists will be established to 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 10.3.1 and Section 10.3.2) will be adjudicated by the Clinical Events Committee. The Clinical Events Committee (CEC) will have the responsibility to adjudicate the classification and category of each reported adverse event. In addition, the CEC will also indicate whether the adverse event is related, possibly related, not related, or has an unknown relation to the Protego lead.

5. DATA COLLECTION

5.1 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 investigational sites, and any other parties authorized by BIOTRONIK.

5.2 CASE REPORT FORMS (CRFS)

Original data will be collected at each investigational site and recorded into the EDC system, audited and monitored by BIOTRONIK, via completion of electronic CRFs (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 Protego 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 Procedure
- Implant Test Values
- Routine Follow-ups (± 30 days)
- Unscheduled Interim Follow-up
- Adverse Event
- System Revision
- Out of Service
- Registry Exit
- Protocol Noncompliance
- Data Clarification

5.3 DATA CLARIFICATION/DATA QUALITY CONTROL

BIOTRONIK will review registry data. At any time, reports can be generated on data completion and missing data for each investigational 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 extensive automatic edit and plausibility checks which provide information to the investigational sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

To ensure protocol compliance at all participating investigational sites, BIOTRONIK monitors will conduct monitoring visits (see Section 7).

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

5.4 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. The EDC system also provides a subject follow-up scheduling tool in the form of a Visit Scheduler Report. This report allows research personnel to become alerted to and track all registry subjects that should be scheduled for upcoming follow-ups. Monitoring visits include a review of subjects that may be lost to follow-up (see Section 7).

5.5 SUBJECT DATA CONFIDENTIALITY

All information sent to BIOTRONIK pertaining to each subject will be kept confidential at BIOTRONIK and is subject to FDA audit. Source documents used to support endpoint adjudication by the CEC in the Protego DF4 registry will have all confidential subject 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.

6. 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.

As with any implantable device, there are always potential risks that accompany the device. The following list provides the potential risks that may occur with the Protego DF4 lead in combination with an ICD or CRT-D device.

- Acceleration of arrhythmias
- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Damage to lead during implant procedure
- Device migration
- Elevated pacing thresholds
- Embolism
- Erosion or pocket erosion
- Extrusion
- Fluid accumulation
- Hematomas, cysts, or fibrotic tissue
- Incomplete lead connection with the pulse generator
- Infection
- Inappropriate detection of ventricular arrhythmias
- Inappropriate therapy, including inappropriate shocks
- Keloid formation
- Lead abrasion and discontinuity
- Lead migration / dislodgment
- Lead fracture / insulation damage
- Lead perforation
- Lead-related thrombosis

- Local tissue reaction / fibrotic tissue formation
- Muscle or nerve stimulation
- Myocardial damage
- Myopotential sensing
- Pacemaker mediated tachycardia
- Pneumothorax
- Potential death due to inability to defibrillate or pace
- Psychological effects (dependency, depression, fear of premature battery depletion, fear of shocking while awake, fear that shocking ability may be lost, anxiety about device resulting from frequent shocks, imagined (phantom) shock)
- Random component failure
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Thromboembolism
- Undersensing of intrinsic signals
- Valvular damage
- Venous occlusion
- Venous or cardiac perforation
- Ventricular ectopy

These risks can be minimized through use of strict aseptic technique, compliance with the registry protocol and technical implant procedures, adherence to the guidelines for selection of subjects, close monitoring of the subject's physiologic status during the implant and follow-up procedures, and by promptly supplying BIOTRONIK with all pertinent information required by this protocol.

BIOTRONIK foresees no additional risks associated with this registry beyond those stated in the labeling for the respective pulse generators and leads.

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/EC review and a subject Informed Consent Form for all after-market research. Monitoring may be conducted on-site at the investigational 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 and documented properly
- 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 unanticipated adverse device effects, 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 investigational plan (protocol), applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB/EC. 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 investigational site.

7.2 REGISTRY MONITORS

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

The address to submit registry information to BIOTRONIK is:

BIOTRONIK, Inc.
Attn: Protego DF4 Registry
Clinical Studies Department
6024 Jean Road
Lake Oswego, Oregon 97035

Registry information may be submitted by fax to: 800 723-9220
For registry assistance, call: 800 547-0394
For technical assistance 24 hours a day, call: 800 547-0394

7.3 MONITORING VISITS

A monitor will conduct monitoring visits at investigational 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 device data and adverse events reported in the EDC system. 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 post-approval 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 study specific equipment and pertinent information in their possession. BIOTRONIK will provide a final report to each investigational site as required by FDA regulations. After FDA has granted approval to terminate this post-approval registry, BIOTRONIK personnel may conduct a registry closure visit according to the monitoring plan. During this 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 completed the registry. Standard patient care will be ensured by the registry site.

9. PROTOCOL COMPLIANCE

The investigator is responsible for conducting the registry in accordance with the signed agreement, the investigational plan (protocol), applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB/EC. The investigator shall notify BIOTRONIK and the reviewing IRB/EC 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 to FDA during interim reports.

9.1 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 endpoints of the registry design

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

9.2 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/EC 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 follow-up window

- Required data not obtained

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

10. 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, Protego lead, right atrial lead, left ventricular lead, or as non-procedure non-system related. For subjects enrolled prior to implant, only adverse events from the first implant attempt onward will be collected.

The investigational site should report each adverse event via an Adverse Event eCRF and provide a copy of the IRB/EC adverse event notification to BIOTRONIK.

10.1 REPORTABLE ADVERSE EVENTS

The following AEs (sorted by classification) will be reported. The classifications listed below are general classifications for site reporting purposes. Detailed information for many classifications is located in Appendix A. The CEC charter may include alternate classifications for some adverse events.

10.1.1 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 implantation of the lead
- 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.)
- Hematoma
- Primary infection
- Lead dislodgement during a procedure (e.g. during pocket revision, device replacement, etc.)
- Lead reversed in header
- Loose set-screw
- Non-healing pocket dehiscence requiring intervention
- Pneumothorax
- Pocket pain
- Pulmonary embolism
- Venous occlusion

10.1.2 Pulse Generator-Related Adverse Events

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

- DF4 header connector malfunction
- DF4 header fluid intrusion
- Device migration
- Premature battery depletion
- Pulse generator failure
- Skin erosion

10.1.3 Lead-Related Adverse Events

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

- Cardiac perforation
- Diaphragmatic/extracardiac stimulation
- High pacing threshold[3]
- Intermittent capture / no lead capture
- Lead conductor fracture
- Lead dislodgement
- Lead impedance out of range, high impedance[4]
- Lead impedance out of range, low impedance[4]
- Lead failure
- Lead oversensing not due to external noise
- Lead oversensing due to external noise
- Lead-related thrombosis
- Lead-related infection
- Lead undersensing or loss of sensing
- Other unexpected complications that are identified through imaging and considered related to the ICD lead or DF4 connector

[3] High pacing threshold is defined as:
A. At implant, threshold that is greater than 3.0V at 0.4ms or 0.5ms, OR

B. At follow-up, threshold that has increased two fold from the chronic (3 month follow-up) threshold value and is greater than 3.5V at 0.4ms or 0.5ms.

[4] Lead impedance out of range is defined as a pacing impedance measurement of ≤ 200 Ohms or ≥ 2000 Ohms or a shock impedance measurement of ≤20 Ohms or ≥150 Ohms.

For each of these lead-related AEs, indicate:

- Confirmed lead integrity failure
- Suspected lead integrity failure
- No lead integrity failure

10.1.4 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:

- Twiddler's syndrome
- Secondary infection
- Ablation sequelae

10.2 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). The CEC will have the responsibility to adjudicate the classification and category of each reported adverse event as implant procedure, implanted pulse generator, lead, or non-procedure non-system related. For each adverse event, the CEC will indicate whether the adverse event relatedness to the Protego lead is: not related, related, possibly related, or unknown.

In evaluation of the two primary endpoints for the post-approval 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 endpoints. The same rules will be used for purposes of Kaplan-Meier survival analyses, described in Section 2.4.2.

Secondary endpoint 3, 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.

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

10.3.1 Adverse Events for the Analysis of Primary Endpoints 1 and 2

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

- Lead pacing polarity or pacing mode reprogrammed due to suspected lead failure.
- Lead abandoned and pacing disabled due to clinical failure or suspected lead failure
- Lead use continued based on medical judgment despite a known clinical failure or suspected lead failure

AEs that are corrected by reprogramming the pulse generator (other than the above) and resolved without invasive action will not be considered an adverse event counted towards the primary endpoints. For example, electrical reprogramming of the pacing polarity to eliminate extra-cardiac stimulation will not be considered an adverse event. Similarly, increasing pacing output as a result of an elevated threshold without further intervention does not count toward the primary endpoint analysis.

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

Primary endpoints 1 and 2 will exclude 1) lead dislodgements that occur within 30 days after lead implant or a lead revision procedure and 2) high pacing threshold, intermittent capture, no lead capture within 30 days after lead implant or a lead revision procedure. However, these will count towards the adverse event secondary endpoint.

In addition, the following two pulse generator-related adverse events will be included in the analysis of primary endpoints 1 and 2: DF4 header connector malfunction and DF4 header fluid intrusion.

10.3.2 Adverse Events for the Analysis of Secondary Endpoint 3

If any of the following invasive actions occur in order to resolve an above listed RA or LV lead-related AE, the AE will be included in the secondary 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 actions occur in order to resolve an above listed RA or LV lead-related AE, the AE will be included in the secondary endpoint analysis:

- Lead pacing polarity or pacing mode reprogrammed due to suspected lead failure.
- Lead abandoned and pacing disabled due to clinical failure or suspected lead failure
- Lead use continued based on medical judgment despite a known clinical failure or suspected lead failure

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

Adverse events excluded from the primary endpoint, as listed in Section 10.3.1, are also included in this secondary endpoint analysis.

10.4 ADVERSE EVENT REPORTING

The adverse events that an IRB/EC considers reportable are dependent on the particular IRB/EC. To avoid underreporting, BIOTRONIK recommends that, at a minimum, the investigator reports the procedure-related, lead-related, and pulse generator-related adverse events that occur during the Protego Post-Approval Registry to BIOTRONIK and the IRB/EC.

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.

11. IRB APPROVAL

Institutional Review Board (IRB) approval is required from each institution prior to participation in this post-approval registry. Subject enrollment may not begin until the IRB and BIOTRONIK have granted approval for the investigational 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.

11.1 OTHER INSTITUTIONS AND PHYSICIANS

This post-approval registry is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK and the appropriate IRB/EC. Additional investigational sites may be included in this registry. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject with a registry device (e.g. when a subject goes to the emergency room for medical treatment). In any such situations, the IRB/EC and the investigator must continue to provide oversight for that subject's medical care and rights as a research subject. BIOTRONIK will ensure that the necessary support personnel are available to any physician providing immediate care for a subject in order to answer questions about the device and provide guidance in collecting the necessary documentation required for the clinical registry.

12. INFORMED CONSENT

Prior to the subject's participation in the investigation, informed consent is required from all subjects. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50). The investigator is required to inform BIOTRONIK and the reviewing IRB/EC within 5 days if any subject was not appropriately consented to participate in the registry. BIOTRONIK is then required to report any failure to obtain subject consent to the FDA within 5 working days of learning of such an event. In order to assist with the consent process, BIOTRONIK will provide a template subject consent form to investigational sites participating in the registry.

13. RECORDS AND REPORTS

13.1 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/EC, BIOTRONIK, a monitor, or the FDA, or any other regulatory authority. (e.g., a letter sent from the investigator to the IRB/EC).
- A copy of the registry protocol
- Signed investigator or research agreement
- Signed Financial Disclosure Form
- A copy of the IRB/EC letter approving the research registry
- A copy of the IRB/EC approved subject Informed Consent Form
- All clinical forms and documentation, including:
    - a copy of the signed subject consent form
    - all supporting documentation for data entered into the EDC system
    - records of any adverse device effect, 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

13.2 INVESTIGATOR REPORTS

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

- Notification of a subject death during the investigation
- Notification of the withdrawal of IRB/EC approval
- Annual progress reports prepared for the IRB/EC
- Notification of any deviations from the investigational plan
- Notification that an informed consent was not obtained from the subject

- Final summary report prepared for the IRB/EC
- Any other information upon the request of an IRB/EC, FDA, or BIOTRONIK

Table 5 outlines the responsibilities, including time constraints, for submitting the above reports.

Table 5: Investigator Reporting Responsibilities

Type of Report	Report to BIOTRONIK	Report to IRB/EC	Time Constraints of Notification
Subject Death During Investigation	Required	Required	BIOTRONIK as soon as possible and as required by reviewing IRB/EC
Adverse Event	Required	IRB/EC dependent	Within 10 calendar days after notification of the event
Unanticipated Adverse Device Effect	Required	Required	Within 10 working days after notification of the effect
Subject Withdrawal	Required		Within 5 working days
Withdrawal of IRB/EC Approval	Required		Within 5 working days
Progress Report	Required	Required	Submitted not less often than yearly
Significant Deviations from Investigational 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

13.3 SPONSOR RECORDS

BIOTRONIK will maintain the following records:

- All correspondence that pertains to the registry with the investigator(s), IRB/EC, and FDA
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB/EC that is involved with the investigation
- Adverse events and complaints
- Adverse device effects (whether anticipated or unanticipated)
- Electronic case report form data
- Completed subject informed consent forms
- Clinical investigation plan and report of prior investigations

- Screening visit reports
- Monitoring reports
- Clinical progress reports
- Statement of the extent to which the good manufacturing practice regulation is part 21CFR820 will be followed in manufacturing the device

13.4 SPONSOR REPORTS

Table 6: Sponsor Reporting Responsibilities

Type of Report	Prepared by BIOTRONIK for	Time Constraints of Notification
Withdrawal of IRB/EC Approval	FDA, all reviewing IRBs/ECs and participating investigators	Within 5 working days of receipt of notice of withdrawal of approval
Withdrawal of FDA Approval	Reviewing IRBs and participating investigators	Notification will be made within 5 working days.
Progress Report	FDA, all reviewing IRBs/ECs	A progress report will be submitted at least annually
Recall and Disposition	FDA, all reviewing IRBs/ECs	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	FDA, all reviewing IRBs/ECs and participating investigators	Notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination of the registry.

APPENDIX A: DEFINITION OF TERMS

AE (Adverse Event) – An unwanted affect detected in participants either implant procedure-related, pulse generator-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 relatedness to the Protego lead is: not related, related, possibly related, or unknown.

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

Cardiac Perforation – Penetration of the lead tip through the myocardium (including microperforation), either clinically suspected or confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram and/or visually.

CEC – Clinical Events Committee

Clinical Failure – Inability of the lead to correctly sense or pace in the heart, not attributable to a mechanical malfunction of the lead or pulse generator that remains unresolved despite reprogramming and/or repositioning.

CFR – Code of Federal Regulations

Conductor Fracture – See Lead Fracture

Confirmed Failure – A lead having clinically relevant characteristics that are outside the performance limits established by BIOTRONIK while implanted and in service, as confirmed by analysis, except for changes in characteristics that are due to induced malfunctions. Lead damage caused during or after explant is not considered a failure.

Chronic Threshold – Chronic threshold is defined as the pacing threshold determined at the subject's 3 month follow-up visit.

eCRF – Electronic Case Report Form

EDC – Electronic Data Capture system

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 Loss of Capture – Intermittent or complete failure to achieve cardiac stimulation at programmed output delivered outside of the cardiac refractory period.

High Pacing Threshold – One of the following definitions must be met:

1. At implant, thresholds for the Protego lead that are greater than 3.0 V at 0.4 ms or 0.5 ms, or

2. At follow-up, pacing thresholds for the Protego lead that have increased two fold from the chronic threshold value, and are greater than 3.5V at 0.4 ms or 0.5 ms.

Insulation Breach/Break – Visual, electrical, or radiographic evidence of a disruption or break in the insulation of a lead.

Intermittent Capture – Ineffective and inconsistent cardiac stimulation at irregular intervals in response to cardiac pacing delivered outside of the cardiac refractory period with a pacing output that exceeds the safety margin (which is twice the measured pacing threshold).

IRB – Institutional Review Board

Lead Dislodgment or Lead Migration – 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 Fracture – Visual, electrical and/or radiographic evidence of mechanical break within the lead conductor (connectors, coils and/or electrodes).

Lead Impedance Out of Range – Pacing impedance is considered abnormal if a measurement is ≤ 200 ohms or ≥ 2000 ohms. Shock impedance is considered abnormal if a measurement is ≤ 20 ohms or ≥ 150 ohms.

Loss of Sensing – Complete failure to sense any intrinsic events that occur outside the programmed refractory periods at programmed sensitivity settings.

LV lead – Left ventricular lead

Non-healing Pocket Dehiscence – Separation of wound edges around the pocket of the implanted pulse generator that have 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 the predicted date.

Mechanical Failure – Malfunction of the lead through a break in the conductor, insulation or connector pin leading to loss of pacing/sensing.

RA lead – Right atrial lead

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

Suspected Generator Failure – Pulse generator issue that is potentially an electrical malfunction.

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.

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

Undersensing – Intermittent failure to sense any intrinsic events that occur outside the programmed refractory period.

APPENDIX B: TIMELINE

The timeline of the Protego DF4 Post-Approval Registry is dependent on the PMA Supplement date, the ability to recruit sufficient number of interested centers and the ability to enroll subjects at an estimated rate of 0.5 subjects/site/month.

Milestone	Window	Estimated Date
Protego DF4 FDA approval	Approval	June 2014
First IRB approval of clinical site	Approval + 4 months	October 2014
First site open to enrollment	Approval + 5 months	November 2014
First subject enrolled	Approval + 6 months	December 2014
5 clinical sites opened to enrollment	Approval + 7 months	January 2015
Enrollment of 10 subjects	Approval + 8 months	February 2015
25 clinical sites opened to enrollment	Approval + 10 months	April 2015
Enrollment of 50 subjects	Approval + 12 months	June 2015
Enrollment of 100 subjects	Approval + 15 months	September 2015
50 clinical sites opened to enrollment	Approval + 17 months	November 2015
75 clinical sites opened to enrollment	Approval + 24 months	June 2016
Enrollment of 500 subjects	Approval + 28 months	October 2016
Enrollment of 1000 subjects	Approval + 41 months	November 2017
Enrollment of 1694 subjects (Enrollment Complete)	Approval + 59 months	May 2019
End of registry based on 5 years follow-up from last-subject-enrolled	Approval + 120 months (10 years)	June 2024
Final report submitted to FDA	Approval + 126 months	December 2024