Assessment of Primary Prevention Patients Receiving An ICD – Systematic Evaluation of ATP

APPRAISE ATP

CLINICAL INVESTIGATION PLAN

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Version AB

Sponsored By

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Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor. A complete listing of applicable vendors will be provided to investigational sites.

Original Release: 18 Jul 2016

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Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	**18Jul2016**	**Template 90702637 Ver. AG**	**N/A**	**Initial Release**	**N/A**
AB	**02Aug2016**	**Template 90702637 Ver. AG**	**Section 11.5: Tables 11.5-1 and 11.5-2**	**Removed column in tables under VT-1 Zone: Rhythm Detection Enhancement On**	**Clarification of programmable parameters**

2. Protocol Synopsis

Assessment of Primary Prevention Patients Receiving An ICD – Systematic Evaluation of ATP (APPRAISE ATP)	
Study Objective(s)	The primary objective is to understand the role of antitachycardia pacing (ATP) in primary prevention patients indicated for ICD therapy. The incidence of all-cause shocks in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.
Planned Indication(s) for Use	All implanted devices will be used within the current labeled indications for use in the applicable geography.
Test Device	All commercially approved Boston Scientific single and dual chamber transvenous ICD (TV-ICD) devices will be included in the trial.
Study Design	APPRAISE ATP is a global, prospective, randomized, multi-center, clinical trial.
Planned Number of Subjects	Approximately 2,600 patients will be enrolled in this trial.
Planned Number of Investigational Sites / Countries	The study will be conducted at up to 200 sites globally.
Primary Endpoint	The primary endpoint is time to first all-cause shock after randomizing subjects to one of the treatment arms.
Additional Endpoints	• All-cause mortality • Time to first appropriate shock • Time to first inappropriate shock • Identification of baseline clinical factors associated with the use of ATP, bradycardia pacing, and the need for future CRT-D pacing therapy

Assessment of Primary Prevention Patients Receiving An ICD – Systematic Evaluation of ATP (APPRAISE ATP)	
Method of Assigning Patients to Treatment	1:1 randomization will occur in the electronic data capture (EDC) system. Subjects will be randomized to ATP and shock, or shock only.

Follow-up Schedule	• Enrollment (occurs ≤ 60 calendar days post successful device implant)
	• Randomization (obtained in the EDC the same calendar day of device programming to randomized arm)
	• Programming to randomized treatment arm (Index procedure day 0)
	  o Device programming must be done the same calendar day of obtaining randomization assignment, and cannot exceed 60 calendar days post implant
	• In clinic follow-up visits for subjects not monitored on LATITUDE:
	  o Every 180±60 calendar day intervals from the Index procedure date (i.e. 180±60 days, 360±60 days, 540±60 days) up to 60 months
	• For subjects who are remotely monitored on LATITUDE:
	  o Annual in-clinic visits, subject phone calls, and device uploads via LATITUDE will be required per the data collection schedule in this protocol.

Study Duration	The trial duration is estimated to be 5.5 years from 1st enrollment to study closure.

Key Inclusion Criteria	• Subject with a Boston Scientific transvenous ICD (de novo implant or upgrade from pacemaker to ICD) implanted because of one of the following:
	  ▪ Prior MI and left ventricular ejection fraction (LVEF) less than or equal to (≤)30% OR
	  ▪ Ischemic or non-ischemic cardiomyopathy, and LVEF ≤ 35% , and NYHA class II or III
	• Subject is age 21or above, or is considered of legal age per given geography
	• Subject is willing and capable of providing informed consent

Assessment of Primary Prevention Patients Receiving An ICD – Systematic Evaluation of ATP (APPRAISE ATP)	
	• Subject is willing and capable of complying with follow-up visits as defined by this protocol
Key Exclusion Criteria	• History of spontaneous sustained VT (≥ 160 bpm at ≥ 30 seconds in duration) or VF not due to a reversible cause • NYHA Class IV documented in the medical records within 90 calendar days prior to enrollment • Subject is eligible and scheduled for cardiac resynchronization (CRT) implant • Subjects with a previous subcutaneous ICD (S-ICD) • Subject with existing TV-ICD device implanted for greater than 60 days • Subjects with coronary artery bypass graft surgery or percutaneous coronary intervention within the past 90 calendar days prior to enrollment • Subjects with documented myocardial infarction within the past 90 calendar days prior to enrollment • Subjects on the active heart transplant list • Subject who has a VAD or is to receive VAD • Life expectancy shorter than 18 months due to any medical condition (e.g., cancer, uremia, liver failure, etc…) • Subjects currently requiring hemodialysis • Subject who is known to pregnant or plans to become pregnant over the course of the trial • Subject is enrolled in any other concurrent clinical study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific
Statistical Methods	
Primary Statistical Hypothesis	The primary endpoint will assess equivalence of the programming schemes, employing a relative equivalence margin of 35% in each direction. H0: Hazard Ratio ≤ 0.65 or Hazard Ratio ≥ (1/0.65) HA: 0.65 < Hazard Ratio < (1/0.65)

Assessment of Primary Prevention Patients Receiving An ICD – Systematic Evaluation of ATP (APPRAISE ATP)	
Statistical Test Method	Cox Proportional Hazards Modeling O'Brien-Fleming group-sequential testing (4 total tests) will be performed, to allow for early stopping if one programming scheme is superior to the other. Overall study alpha will equal 5%.
Sample Size Parameters	Total Sample size = 2600 subjects (1300 per group) • Expected all-cause shock rate in each group = 7% • 5% alpha • Power ≥ 90% • Equivalence Margin = (0.65 – [1/0.65]) = (0.65 – 1.54) • Attrition at 18 months = 10% • Estimated enrollment period = 42 months • Expected Follow-up period = minimum of 18 months for last patient enrolled to maximum of 60 months for first patient enrolled

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

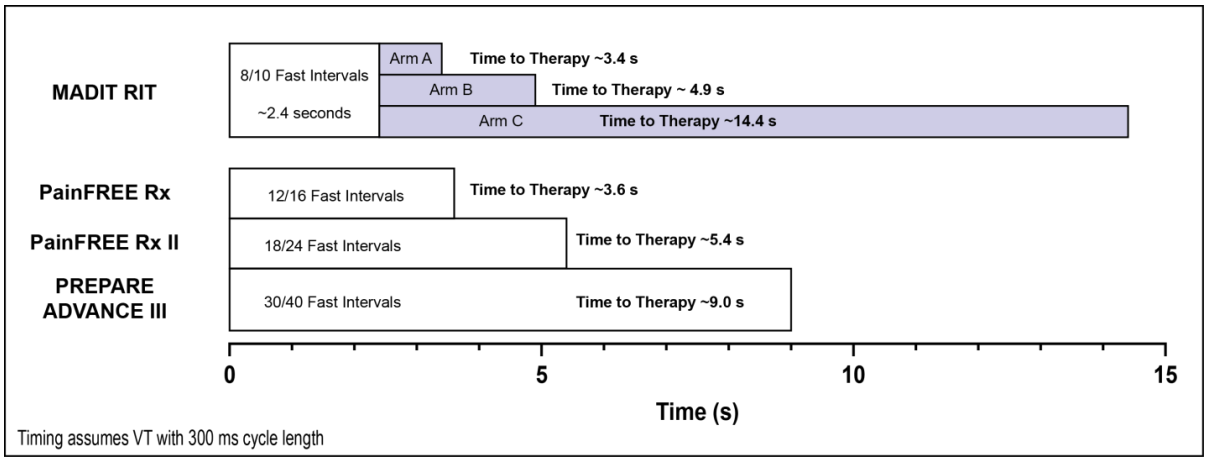
4. Introduction

Antitachycardia pacing (ATP) is programmed electrical stimulation delivered by an implantable cardioverter defibrillator (ICD) that is intended to terminate re-entrant ventricular tachycardia (VT). Non-randomized trials of ICDs in the early 1990s demonstrated the safety and efficacy of ATP in secondary prevention patients, that is, patients with a history of ventricular tachyarrhythmias. ATP has been shown to be valuable in terminating potentially lethal ventricular tachyarrhythmias without shocks.[1, 2, 3] Success in terminating VT was achieved in approximately 90% of patients. In 2-4% of patients, however, ATP accelerated VT into ventricular fibrillation (VF), requiring a shock for arrhythmia termination.

Three studies were to follow that expanded the indications for use of ICDs beyond those patients with a history of VT/VF: MADIT[4], MADIT II[5], and SCD-HeFT[6]. MADIT was designed and initiated in 1991 before ATP was commercially available and consequently was not designed to study ATP use. MADIT II allowed physicians to program devices according to investigator discretion and many did program it on. Although ATP successfully terminated VT in some patients, it was not programmed in a systematic way in MADIT II and the study results were not prospectively designed for analysis. In SCD-HeFT, devices were programmed to deliver shocks alone and the use of ATP was not permitted. Thus, while these studies made ICDs available to a wider population, they did not provide medical evidence to help guide the use of ATP.

Different manufacturers have different programming methods for determining the time to delivery of ATP. Figure 1 compares the timing used in the MADIT-RIT study[7] , using Boston Scientific devices, to other studies of ATP performed using Medtronic devices to permit comparisons of the time to therapy delivery delays between studies under the assumption that the detected tachyarrhythmia has a 300 ms cycle length. Both manufacturers employ algorithms in which a programmable number of pre-defined fast intervals must be detected before therapy is delivered. The Boston Scientific devices used in MADIT-RIT were capable of being programmed to permit an incremental duration delay above and beyond that needed to declare the presence of tachyarrhythmia requiring treatment. Note that this table provides the approximate time to initiation of therapy only. The time to complete delivery of ATP and confirm that the rhythm has been successfully converted may add an additional 2-3 seconds.

Figure 1: Comparison of Programmed Detection Delays for ATP Delivery



Studies undertaken that elucidate the role of ATP are summarized as follows:

MADIT-RIT[8] : The MADIT-RIT study was designed to test whether inappropriate shocks in primary prevention patients could be reduced through at least one of two treatment strategies when compared to a third control arm consisting of patients with conventional programming: increasing the rate cutoff (high rate therapy) or prolonging the time before delivering device therapy (delayed therapy). Patients were enrolled in MADIT-RIT from September 2009 through October 2011 and were followed for a mean of 1.4 years and the use of both CRT-D devices (50%) and ICDs (50%) were permitted. Both strategies were successful in reducing the risk of occurrence of first inappropriate ICD therapy, with high rate therapy associated with a 79% reduction ($p<0.001$) and delayed therapy associated with a 76% reduction ($p<0.001$). Furthermore, MADIT-RIT demonstrated that both programming strategies can be employed without increasing all-cause mortality or syncope.

Examination of appropriate ATP delivered in MADIT-RIT revealed 446 episodes in the convention programming arm, compared to 113 episodes in the high rate therapy arm and 143 episodes in the delayed therapy arm. The authors noted that this finding suggests that much of the ATP delivered in the conventional programming arm was prematurely delivered for non-sustained ventricular tachyarrhythmias. The delivery of ATP in these instances, while consistent with the programming of the device may also be clinically unnecessary.

PainFREE Rx II[9]: PainFREE Rx II, preceded by the PainFREE Rx[10] pilot study, was designed to determine whether fast VT, defined as ventricular rhythms detected between 188-250 bpm, could be successfully and safely treated with ATP. The primary outcome measure was ATP effectiveness. This study enrolled patients from January 2001 to March 2002 and included a mix of patients with secondary indications and MADIT indications but ceased enrollment prior to the availability of ICD indications for the MADIT II and SCD-HeFT populations. Patients were randomized to two arms: one arm received ATP for fast VT with detection of 18/24 fast intervals with a rate cutoff of 188 bpm while the other arm was randomized to shocks only using the same rate cutoff of 188 bpm. After 11 months of follow-up, ATP was found to have successfully terminated 229/284 episodes of fast VT (81% unadjusted, 72% after adjusting for multiple events) and it was considered to be safe in

this population as well without an appreciable increase in syncope, mortality, episode duration, or acceleration.

PREPARE[11]: The PREPARE study was a one-armed observational study that compared the effect of prolonged detection intervals on a morbidity index, which was a composite of all-cause shocks delivered to treat spontaneous episodes, syncope of arrhythmic or presumed arrhythmic origin, and untreated sustained symptomatic VT/VF events. The control group was a historical cohort taken from the MIRACLE ICD and EMPIRIC studies. Patients enrolled in PREPARE were programmed to a detection interval of 30/40 fast beats with a rate cutoff of 182 bpm. All patients enrolled were from a primary prevention population and patients were implanted with either CRT-D devices (35%) and ICDs (65%). The enrollment period extended from October 2003 through May 2005. The mean follow-up was not reported, but patients were followed for a minimum of 12 months. The authors reported a significant reduction in the morbidity index, from 0.26 events/year in the PREPARE cohort and 0.69 events/year in the historical cohort (p=0.003).

ADVANCE III [12]: This study tested the hypothesis that further prolongation of the delay prior to initiating therapy may reduce ICD therapies, consisting of both shock and ATP delivery. Patients were enrolled from March 2008 to December 2010 and considered of both secondary and primary prevention patients (25% and 75%, respectively) as well as both CRT-D devices and ICDs (41% and 59%, respectively). Patients were randomized to one of two arms: ATP delivery with standard detection parameters (18/24 intervals as studied in PainFREE Rx II) versus ATP delivery with long detection parameters (30/40 fast intervals). Rate cutoffs of 188 bpm were used in both arms. Assuming a ventricular tachyarrhythmia with a 300 ms cycle length, this analysis in effect compared a 5.4 second to a 9.0 second delay. After an average follow-up interval of 12 months, the authors reported a 37% reduction in the incidence of a composite of shock and ATP therapies (p<0.001) that was driven predominantly by a 42% reduction in the incidence of ATP alone (p<0.001). The reduction in the incidence of shocks approached but did not achieve statistical significant (23%, p=0.06). The authors concluded that a strategy of prolonged device detection significantly reduced the rate of ICD therapies.

The MADIT-RIT study was not prospectively designed to assess the role of ATP, but analysis of the two types of ICD therapies revealed that the incidence of shocks, whether appropriate or inappropriate, was consistent across all three arms (~5% and ~3% for appropriate and inappropriate shocks, respectively) with no significant difference in shock rates. Both of the new treatments strategies were associated with substantial reductions in ATP, however. The incidence of appropriate and inappropriate ATP in the control group (18% and 17%, respectively) were significantly less with high rate therapy (5% appropriate and 2% inappropriate, p<0.001) and with delayed therapy (2% appropriate and 3% inappropriate, p<0.001). An analysis of mortality in MADIT-RIT[13] revealed a statistically significant association between inappropriate ATP and all-cause mortality [hazard ratio = 3.25, 95% confidence interval (1.33-7.94), p=0.10] while no association was found between appropriate ATP and all-cause mortality [hazard ratio=1.02, 95% confidence interval (0.36-2.88), p=0.977]. An association does not necessarily imply causality, however, and further investigation into ATP is warranted.

We conclude from these reports in the medical literature that the value of ATP in primary prevention patients who receive ICDs is uncertain. ATP success as previously reported potentially includes a large proportion of patients who receive unnecessary ATP for non-sustained VT. Although a small proportion of patients do appear to derive long-term benefit from ATP, other patients may also receive shocks following inappropriate ATP. Accordingly, it is hypothesized that a strategy of programming prolonged delay prior to initiating therapy may find that the benefit of appropriate ATP is offset by the consequences of inappropriate ATP. This study is designed to confirm this hypothesis in a large prospective randomized controlled trial.

5. Device Description

5.1. *Medical Equipment Description*

Commercially approved Boston Scientific (BSC) single and dual chamber transvenous (TV) ICD devices and future generations of BSC single and dual TV-ICD devices approved by the appropriate regulatory bodies will be included in the trial. Any commercially available lead from any manufacturer is eligible for implantation in the study.

6. Study Objectives

The primary objective is to understand the role of ATP in primary prevention patients indicated for ICD therapy. The incidence of all-cause shocks in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.

Multivariate analyses will also be performed to determine which baseline clinical factors are associated with the use of ATP, bradycardia pacing, and the need for CRT-D pacing therapy.

7. Study Endpoints

The primary endpoint collected post randomization is:

- Time-to-First All-Cause Shock

The secondary endpoints are:

- Time-to-First All-Cause Shock or Death from Any Cause
- Time-to-Death from Any Cause
- Time-to-First Appropriate Shock
- Time-to-First Inappropriate Shock

The tertiary objective is a multivariate analysis to determine covariates associated with the use of ATP, bradycardia pacing, and the need for future CRT-D pacing therapy.

8. Study Design

This is a global, prospective, randomized, multi-center clinical trial that has been classified as a non-mandated post market trial.

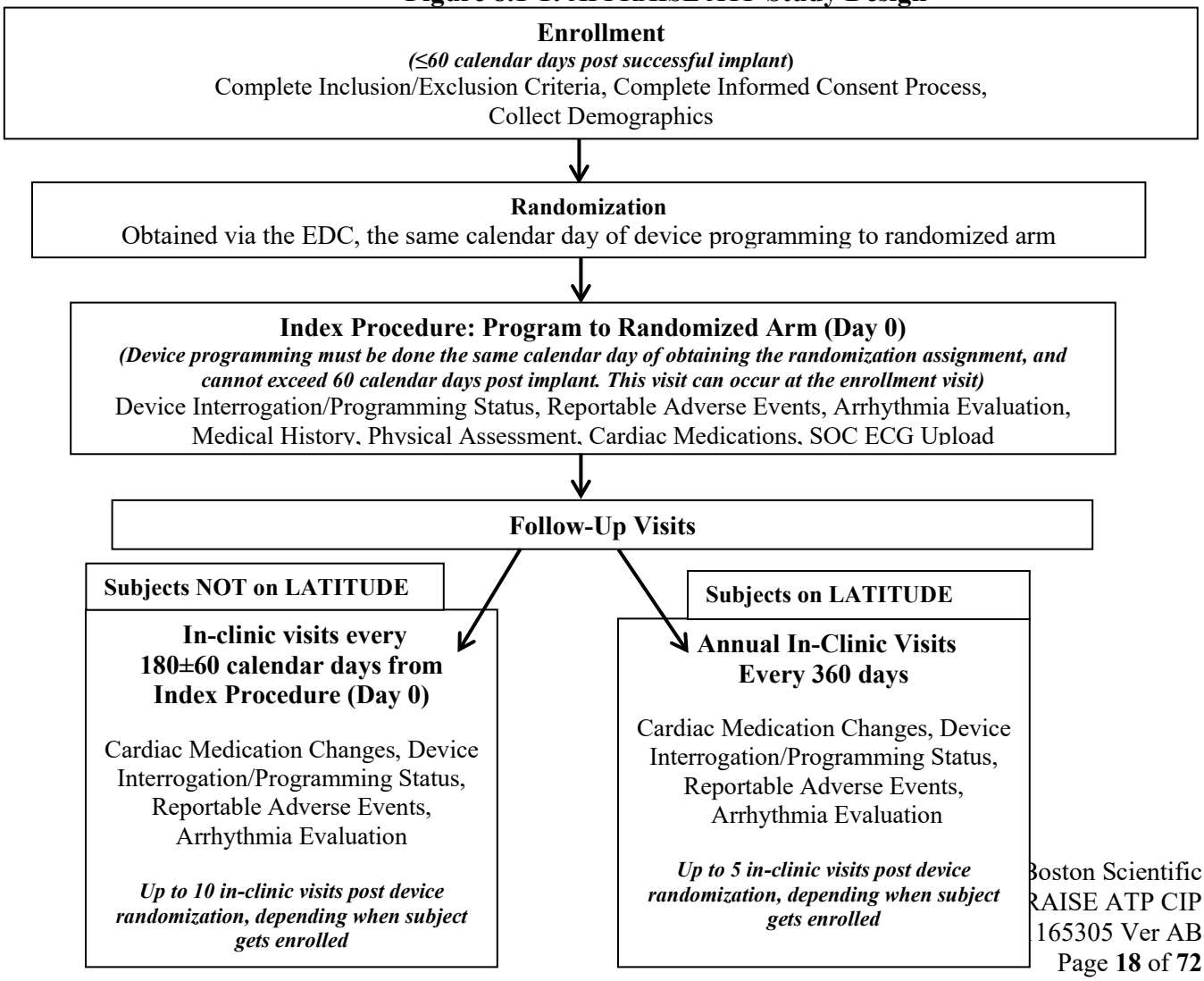
8.1. *Scale and Duration*

The study will be conducted at up to 200 sites globally. Approximately 2,600 subjects will be enrolled, and sites may continue to enroll subjects until notified of enrollment completion.

Subjects will be consented for follow up visits through 60 months (5 years). Their length of participation will differ depending when they entered the study. Sites will continue to follow subjects until notified of follow-up completion.

The study will conclude after the earliest of one of following occurrences: (1) one arm is determined to be superior at one of the three interim analyses (per Section 12.3.1), or (2) a sufficient number of shock episodes have occurred to sufficiently power the primary endpoint. Under current assumptions, it is expected that the last enrolled patient will be followed for approximately 18 months and the first enrolled patient will be followed for approximately 60 months.

Figure 8.1-1: APPRAISE ATP Study Design



8.2. *Treatment Assignment*

Any patient meeting all inclusion and no exclusion criteria is enrollment eligible for the APPRAISE ATP study. Patients are considered enrolled in the study once the informed consent form (ICF) has been executed.

Randomization schemes can be obtained by logging onto the electronic data capture system (EDC) and registering the patient. Randomization will be in a 1:1 ratio of either treatment arm and will be stratified by ischemic etiology, history of atrial fibrillation, and diabetes.

8.2.1. Treatment Arms

There will be two treatment arms of the trial:

Arm 1: **ATP and Shock** OR Arm 2: **Shock Only**

Table 8.2-2 Treatment Arms

ARM 1= ATP and Shock	ARM 2 = Shock Only
Zone 1: Monitor Only (VT-1) • 170 bpm, monitor only • Disable therapy **Zone 2 (VT)** • 200 bpm, 12s delay • ATP x 1 burst of 8 pulses • Shocks 41J **Zone 3 (VF)** • 250 bpm, 5s delay • Shocks 41J	**Zone 1: Monitory Only (VT-1)** • 170 bpm, monitor only • Disable therapy **Zone 2 (VT)** • 200 bpm, 12s delay • Shocks 41J **Zone 3 (VF)** • 250 bpm, 5s delay • Shocks 41J

8.3. *Justification for the Study Design*

The APPRAISE ATP study is designed to assess the incidence of all cause shocks in patients who have an indication for primary prevention of sudden cardiac death and a low ejection fraction that are implanted with a commercially available BSC TV-ICD (single or dual chamber) device. The study is intended to determine the value of ATP in this patient population utilizing current programming guidelines of higher rates and longer delays[15, 16]

9. Subject Selection

9.1. *Study Population and Eligibility*

Primary prevention is an indication for an ICD to prevent sudden cardiac death (SCD). It refers to ICDs in individuals who are at risk for, but have not yet had, an episode of sustained VT, VF, or cardiac arrest.[14] The study population for the APPRAISE ATP trial consists of patients who meet the guidelines[14] for ICD therapy for primary prevention patients.

Only primary prevention patients who have had a successful implant of a BSC single or dual chamber TV-ICD will be enrolled. The Investigator is responsible for screening all patients to determine eligibility of the trial.

9.2. *Inclusion Criteria*

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

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	• Subject with a Boston Scientific transvenous ICD (de novo implant or upgrade from pacemaker to ICD) implanted because of one of the following: ▪ Prior MI and left ventricular ejection fraction (LVEF) less than or equal to (≤)30% OR ▪ Ischemic or non-ischemic cardiomyopathy, and LVEF ≤ 35% , and NYHA class II or III • Subject is age 21or above, or is considered of legal age per given geography • Subject is willing and capable of providing informed consent • Subject is willing and capable of complying with follow-up visits as defined by this protocol

9.3. *Exclusion Criteria*

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

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	• History of spontaneous sustained VT (≥ 160 bpm at ≥ 30 seconds in duration) or VF not due to a reversible cause • NYHA Class IV documented in the medical records within 90 calendar days prior to enrollment • Subject is eligible and scheduled for cardiac resynchronization (CRT) implant • Subjects with a previous subcutaneous ICD (S-ICD) • Subject with existing TV-ICD device implanted for greater than 60 days • Subjects with coronary artery bypass graft surgery or percutaneous coronary intervention within the past 90 calendar days prior to enrollment • Subjects with documented myocardial infarction within the past 90 calendar days prior to enrollment • Subjects on the active heart transplant list • Subject who has a VAD or is to receive VAD • Life expectancy shorter than 18 months due to any medical condition (e.g., cancer, uremia, liver failure, etc…) • Subjects currently requiring hemodialysis • Subject who is known to pregnant or plans to become pregnant over the course of the trial • Subject is enrolled in any other concurrent clinical study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects who meet the eligibility criteria and agree to participate will be given written informed consent approved by the center's Institutional Review Board (IRB) / Ethics Review Committee (ERC).

All subjects who complete the informed consent process, sign and date the informed consent form are considered enrolled in the APPRAISE ATP study. No study related procedures can take place until the ICF is signed. Screening tests that are part of Standard of Care (SOC) can

be used to determine pre-eligibility. Subjects enrolled in this investigation must be followed per this investigational protocol.

10.2. *Withdrawal*

All subjects enrolled in the clinical study, including those withdrawn from the clinical study or lost to follow-up, shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. Reasons for withdrawal include, but are not limited to:

- Subject found not to meet eligibility criteria
- Subject did not get randomized
- Subject choice to withdraw consent
- Device explanted and not replaced with a BSC TV-ICD
- Subject was upgraded to a CRT-D system
- VAD insertion or heart transplant
- Investigator discretion
- Enrollment ceiling met
- Lost to follow-up, despite best efforts to locate the subject;
    - Three documented attempts to contact the subject, including one certified letter, are required to declare a subject lost to follow up.
- Death (see Section 19.7 for reporting requirements)

If a subject withdraws from the clinical investigation, the reason(s) shall be reported on the End of Study electronic case report form (eCRF) in the EDC system. Data up to the point of withdrawal will be collected. All open adverse events should be closed or documented as chronic. Normal manufacturer vigilance monitoring of device performance will take place after a subject is withdrawn.

10.3. *Subject Status and Classification*

All subjects who complete the informed consent process, sign and date the ICF are considered enrolled. Subject status will be classified as below after enrollment:

Intent: Refers to a subject who meets all eligibility and signs the consent, but does not get randomized. This classification status also refers to:

- A subject who no longer meets eligibility criteria at the time of randomization
- A subject who is no longer willing to participate in the study

The original ICF and screening documentation for intent subjects must be maintained in the Center's files and an End of Study form is to be completed. Patients shall be withdrawn from the study and followed per standard of care. No further follow-up is required. Intent patients will not count towards the enrollment ceiling.

Treatment: Refers to a subject who has been enrolled and their device has been reprogrammed to the arm that they have been randomized to (ATP and Shock or Shock Only.)

10.4. *Enrollment Controls*

Each center may enroll up to a maximum of 260 subjects. If a center wishes to exceed this limit, the center must obtain prior written approval from the sponsor or sponsor's delegated representative.

Subjects consented, but who do not undergo a randomization/programming to either treatment arm, will not count towards the 2,600 patients. Patients already consented at time of notification shall still be entered in the database and withdrawn from the study.

Investigational sites will be notified when the enrollment goal is close to being reached and once enrollment is complete.

11. Study Methods

11.1. *Data Collection*

The data collection schedule for this study is aligned with standard of care (SOC) practices at centers. Therefore, there are two data collection schedules for subjects: 1.) Subjects who are not monitored on LATITUDE and 2.) Subjects who are monitored on LATITUDE.

Table 11.1-1 for subjects who are NOT monitored on LATITUDE

Table 11.1-2 for subjects who are monitored on LATITUDE

Table 11.1-1 Data Collection Schedule – Subjects NOT on LATITUDE

Procedure/ Assessment	Enrollment (≤ 60 calendar days post successful implant)	Randomization (Obtained day of device programming to assigned treatment arm)	Programing to Assigned Treatment Arm *(Day 0)* (Day of randomization. Cannot exceed 60 calendar days post implant)	Follow Up Visits through 5 years 6 Mo: 180±60 d 12 Mo: 360±60d 18 Mo:540±60d 24 Mo: 720±60 d 30 Mo: 900±60d 36 Mo: 1080±60d 42 Mo: 1260 ±60 d 48 Mo: 1440 ± 60d 54 Mo: 1620± 60d 60 Mo: 1800+30d	Unscheduled Visits (within 30 calendar days of therapy delivery)
Informed consent process, including informed consent signature and date	**X**				
Inclusion/Exclusion	**X**	◊			
ECG Upload– Standard of Care (recommended not required)			**SOC**		
Physical assessment			**X**		
Demographics	**X**				
Medical History			**X**		
Cardiac Medications			**X**	**X****	**X****
Randomization – obtained via the EDC system/Risk Stratifiers		**X**			
Device Interrogation/ Programming Status			**X**	**X**	**X**
Reportable AE's		*	*	*	*
Arrhythmia Episodes		*	*	*	*

Legend: X= Required; *=Data required only if the event occurred; **SOC**=Recommended if Center Standard of Care, **= Need to document changes to cardiac meds only, ◊= Sites must verify subject still meets inclusion/exclusion criteria prior to randomization

Table 11.1-2 Data Collection Schedule – Subjects ON LATITUDE

Procedure/Assessment	**Enrollment** (≤60 calendar days post implant)	**Randomization** (Obtained day of device programming to assigned treatment arm)	**Programing to Assigned Treatment Arm** ***(Day 0)*** (Day of randomization. Cannot exceed 60 calendar days post implant)	**LATITUDE Follow Up Data (Automatic Device Report Upload)** Done by Sponsor 6 Mo: 180±60 d 18 Mo:540±60d 30 Mo: 900±60d 42 Mo: 1260 ±60 d 54 Mo: 1620 ±60d	**Subject Phone Call Visit** Done by Center 6 Mo: 180±60 d 18 Mo:540±60d 30 Mo: 900±60d 42 Mo: 1260 ±60 d 54 Mo: 1620 ±60d	**Follow Up Visits (In Clinic)** 12 Mo: 360±60d 24 Mo: 720±60 d 36 Mo: 1080±60d 48 Mo: 1440 ± 60d 60 Mo: 1800+30d	**Unscheduled Visits** (per Physician Discretion as SOC)
Informed consent process, including informed consent signature and date	**X**						
Inclusion/Exclusion	**X**	◊					
ECG Upload – Standard of Care (recommended, not required)			**SOC**				
Physical assessment			**X**				
Demographics	**X**						
Medical History			**X**				
Cardiac Medications			**X**		**X****	**X****	**X****

Randomization – obtained via the EDC system/Risk Stratifiers		**X**					
Device Interrogation/ Programming Status			**X**	**LAT**		**X**	**X**
Reportable AE's		*****	*****		*****	*****	*****
Arrhythmia Episodes		*****	*****	**LAT***		*****	*****

Legend: X= Required; *****=Data required only if the event occurred**; SOC**=Recommended if Center Standard of Care; **LAT**= Required if subject is on LATITUDE remote monitoring. Report will be uploaded by Latitude BSC team; ******= Need to document changes to cardiac meds only;

◊ = Sites must verify subject still meets inclusion/exclusion criteria prior to randomization

11.2. *Study Candidate Screening*

Any subject meeting all of the inclusion criteria and not meeting any of the exclusion criteria is enrollment eligible for the APPRAISE ATP study. A formal screening log is not required to be maintained.

11.3. *Informed Consent and Enrollment*

Subjects who meet all of the inclusion criteria, none of the exclusion criteria, and undergo the informed consent process, sign, and date the informed consent form are considered enrolled in the study. No data collection, data entry, or study specific procedure shall be performed prior to having appropriately consented the patient. Table 11.3.-1 lists the data collection requirements at the enrollment visit.

Table 11.3-1: Source Documentation Requirements – Enrollment Visit

Data Collection Requirement	Retention of Original Source Documentation
• Informed Consent Form and process, including informed consent and signature date • Inclusion/Exclusion Criteria • Demographics	Investigational Center

11.4. *Randomization Assignment*

Randomization by the EDC system and device programming to randomized treatment arm can be performed at the enrollment visit once the patient has completed the informed consent process. Randomization will be obtained through the EDC system. Subject data regarding ischemic etiology, history of atrial fibrillation and diabetes must be entered in the EDC database as randomization cannot occur without these three data points.

If randomization and subsequent device programming to randomized arm is not performed at the enrollment visit, the randomization and device programming visit must occur on the same day, and cannot exceed 60 calendar days post implant. Prior to randomization, sites need to verify that subjects still meet inclusion criteria and no exclusion criteria.

Every reasonable attempt will be made to have subjects blinded to their randomized treatment arm assignment throughout the trial.

Table 11.4-1: Source Document Requirements – Randomization

Data Collection Requirement	Retention of Original Source Documentation
• Subject randomization assignment • Reportable AE's, if applicable	Investigational Center

11.5. *Programming to Treatment Arm – Index Procedure (Day 0)*

If the subject's device was not programmed to the randomized treatment arm assignment at the enrollment visit, programming to the randomized arm must be done the same calendar day of obtaining the randomization assignment, and cannot exceed 60 calendar days post implant. The date the device was programmed to the randomized arm will be considered the time of origin: Index Procedure Day 0, for the subject. Subsequent follow up visits will be based off of this date. Once a subject is programmed to the randomized arm, the subject will remain in the assigned treatment arm until the end of the study to follow the methodology of intention-to-treat (ITT).

Tasks to be performed at this visit include:

- Pulse generator interrogation with routine lead evaluation on implanted RA and RV leads which includes:
    - Intrinsic sensing (mV)
    - Pacing impedance (Ω)
    - Shock lead impedance (Ω)
    - Pacing threshold (V) (pulse width at physician discretion)
- Arrhythmia logbook evaluation
    - Verify subject has not had any spontaneous ventricular rhythms that were treated with a shock
- Programming the device to the subject's randomized treatment arm

Devices are required to be programmed according to this protocol. Table 11.5-1 represents the required device programming for subjects who are randomized to Arm 1: ATP and Shock.

Table 11.5-1: Required Programming: Arm 1: ATP and Shock

ARM 1 = ATP and Shock	Programming
Ventricular Zones	3
Zone 1: (VT-1) Rate	170 bpm
Zone 1: (VT-1) Initial Duration	12 seconds
Zone 1: (VT-1) Therapy	Monitor Only (disable all therapy)
Zone 2: (VT) Rate	200 bpm
Zone 2: (VT) Initial Duration	12 seconds
Zone 2: (VT) Redetection Duration	1.0 second (nominal)
Zone 2: (VT) Post-Shock Duration	1.0 second (nominal)
Zone 2: (VT) Rhythm Detection Enhancement Type	ON (Detection enhancement type is per Investigator Discretion)
Zone 2: (VT) Therapy	All shocks: 41 Joules
ATP1	
Number of Bursts	1
Pulses per Burst	--
Initial	8
Increment	0
Coupling Interval	88%
Burst Cycle Length	88%
Ramp Decrement	0
Minimum Interval	220 ms
ATP2	**OFF**
Zone 3: (VF) Rate	250
Zone 3: (VF) Initial Duration	5 seconds
Zone 3: (VF) Redetection Duration	1.0 second
Zone 3: (VF) Post-Shock Duration	1.0 second
Zone 3: (VF) QUICK CONVERT ATP	**OFF**
Zone 3: (VF) Therapy	All shocks: 41 Joules

Table 11.5-2 represents the required device programming for subjects who are randomized to Arm 2: Shock only.

Table 11.5-2: Required Programming: Arm 2: Shock Only

ARM 2 = Shock Only	Programming
Ventricular Zones	3
Zone 1: (VT-1) Rate	170 bpm
Zone 1: (VT-1) Initial Duration	12 seconds
Zone 1: (VT-1) Therapy	Monitor Only (disable all therapy)
Zone 2: (VT) Rate	200 bpm
Zone 2: (VT) Initial Duration	12 seconds
Zone 2: (VT) Redetection Duration	1.0 second (nominal)
Zone 2: (VT) Post-Shock Duration	1.0 second (nominal)
Zone 2: (VT) Rhythm Detection Enhancement Type	ON: (Detection enhancement type is per Investigator Discretion)
Zone 2: (VT) Therapy	All shocks: 41 Joules
ATP1	**OFF**
ATP2	**OFF**
Zone 3: (VF) Rate	250 bpm
Zone 3: (VF) Initial Duration	5 seconds
Zone 3: (VF) Redetection Duration	1.0 second
Zone 3: (VF) Post-Shock Duration	1.0 second
Zone 3: (VF) QUICK CONVERT ATP	**OFF**
Zone 3: (VF) Therapy	All shocks: 41 Joules

Bradycardia Pacing: Brady pacing programming in either treatment arm will be at the Investigator Discretion. It is recommended that brady programming for single chamber devices is VVI 40 and for dual chamber devices DDD with RHYTHMIQ™ or AV Search + (± rate response).

Source data requirements at Index Procedure: Programming to Treatment Arm is described in Table 11.5-3.

Table 11.5-3: Source Documentation Requirements – Index Procedure (Day 0) Programming to Treatment Arm Visit

Data Collection Requirement	Retention of Original Source Documentation
• Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable • Physical Assessment • Medical History • Cardiac Medications	Investigational Center
• Device Follow Up Report • Selected Episode Electrograms, as applicable • Device Settings Report • Settings Change Report • Arrhythmia log book	Printed copy of all final reports retained at Investigational Center Save to USB for Investigational Site. Copy will be sent to sponsor, if applicable Upload USB into EDC system
• Baseline ECG – most recent, SOC* * NOTE: An ECG is not required to be performed. It is highly recommended that the patient's most recent ECG, performed as SOC, be uploaded into the EDC system as available.	Upload ECG into EDC system if available

11.6. *Semi-Annual Follow-up Visits*

11.6.1 Subjects who are <u>NOT</u> monitored on LATITUDE:

After programming to treatment arm (Index procedure: Day 0), scheduled in-clinic visits are required to be performed at 180 day intervals (± 60days) from the programming (Day 0) date (i.e. 6 Mo: 180±60d; 12 Mo: 360±60d; 18 Mo: 540±60d, etc.) in order to capture new, not previously reported:

- Ventricular arrhythmia episodes
- Reportable adverse events

- Device programming changes
- Protocol deviations
- Device Deficiencies
- Cardiac medication changes

Tasks to be performed at the in-clinic follow-up visits include:

- Pulse generator interrogation with routine lead evaluation on implanted RA and RV leads which includes:
    - Intrinsic sensing (mV)
    - Pacing impedance (Ω)
    - Shock lead impedance (Ω)
    - Pacing threshold (V) (pulse width at physician discretion)
- Arrhythmia logbook evaluation
    - Print applicable arrhythmia episodes
- Save interrogation session to USB
- Upload into EDC system

Source data requirements at the Semi-Annual Follow-Up Visits for subjects who are not monitored on LATITUDE are described in Table 11.6-1

Table 11.6-1: Source Documentation Requirements - Follow Up Visits Subjects NOT on LATITUDE

Data Collection Requirement	Retention of Original Source Documentation
• Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable • Cardiac Medication Changes	Investigational Center
• Device Follow Up Report • Selected Episode Electrograms, as applicable • Device Settings Report • Settings Change Report	Printed Copy of all final reports retained at Investigational Center Save to USB for Investigational Site. Copy will be sent to sponsor, if applicable

Table 11.6-1: Source Documentation Requirements - Follow Up Visits
Subjects NOT on LATITUDE

Data Collection Requirement	Retention of Original Source Documentation
• Arrhythmia log book	Upload USB into EDC system

11.7. *Subjects who <u>are</u> monitored on LATITUDE*

For subjects who are remotely monitored, the wireless LATITUDE™ Patient Management system will be utilized to collect and store treated tachyarrhythmia episodes. Alerts, diagnostic data, and all treated ventricular episodes EGMs are collected for endpoint evaluation directly from the LATITUDE database. Applicable reports will be uploaded remotely into the study database from the LATITUDE BSC team as defined on the data collection schedule on Table 11.1-2.

After programming to treatment arm (Index procedure Day 0), subjects who are remotely monitored with the LATITUDE system must have the following yellow alerts programmed on in the LATITUDE database:

- Ventricular shock therapy delivered to convert arrhythmia
- Accelerated ventricular arrhythmia episode
- Atrial Arrhythmia burden of at least {>1, 3, 6, 12, 18, or 24} hours in a 24 hour period
- Patient triggered event stored

If the HeartLogic feature is available in the implanted device, all subjects with this feature will be monitored by the LATITUDE BSC team for the specific HeartLogic alerts. In the event of an alert, a report will be uploaded by the LATITUDE BSC team into the study database.

Table 11.7-1: LATITUDE Follow Up Data – Device Report Upload

Data Collection Requirement	Retention of Original Source Documentation
• LATITUDE Nominal Device Report • Ventricular arrhythmia episodes • LATITUDE Alerts	Reports uploaded into the study database by BSC LATITUDE team

11.7.1. Phone Call Visits for Subjects ON LATITUDE

Subject phone call visits are required in conjunction with the LATITUDE data device report upload visit. The data to be collected at the subject phone call visit include:

- An assessment of cardiac medication changes
- An assessment of reportable adverse events
- An assessment of device deficiencies

Source data requirements at the subject phone call visits for subjects who are monitored on LATITUDE are described in Table 11.7-2.

Table 11.7-2: Source Documentation Requirements: Subject Phone Call Visit

Data Collection Requirement	Retention of Original Source Documentation
• Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable • Cardiac Medication Changes	Investigational Center

11.7.2 Annual Follow-Up Visits for Subjects monitored on LATITUDE

For subjects monitored on LATITUDE, annual in-clinic visits are required to be performed per the data collection schedule on Table 11.1-2.

Tasks to be performed at the annual in-clinic follow-up visits include:

- Pulse generator interrogation with routine lead evaluation on implanted RA and RV leads which includes:
    - Intrinsic sensing (mV)
    - Pacing impedance (Ω)

  - Shock lead impedance (Ω)
  - Pacing threshold (V) (pulse width at physician discretion)
- Arrhythmia logbook evaluation
  - Print applicable arrhythmia episodes
- Save interrogation session to USB
- Upload into EDC system

Table 11.7-3: Source Documentation Requirements: Annual Follow Up Visits for Subjects on LATITUDE

Data Collection Requirement	Retention of Original Source Documentation
• Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable • Cardiac Medication Changes	Investigational Center
• Device Follow Up Report • Selected Episode Electrograms, as applicable • Device Settings Report • Settings Change Report • Arrhythmia log book	Printed Copy of all final reports retained at Investigational Center Save to USB for Investigational Site. Copy will be sent to sponsor, if applicable Upload USB into EDC system

11.8. *Unscheduled Visits: ICD Interrogation and Evaluation after ICD therapy*

After a patient reports ICD therapy, an in-clinic visit must be scheduled within 30 calendar days, or as soon as possible. The following is required to be collected at all unscheduled in-clinic visits:

- Ventricular arrhythmia episodes
- Reportable adverse events
- Medication changes

- Device programming changes
- Protocol deviations
- Device Deficiencies

Tasks to be performed at the unscheduled visit include:

- Pulse generator interrogation with routine lead evaluation on implanted RA and RV leads which includes:
    - Intrinsic sensing (mV)
    - Pacing impedance (Ω)
    - Shock lead impedance (Ω)
    - Pacing threshold (V) (pulse width at physician discretion)
- Arrhythmia logbook evaluation
    - Print applicable arrhythmia episodes
- Save interrogation session to USB
- Upload into EDC system

Table 11.8-1: Source Documentation Requirements: Unscheduled Visits: ICD Interrogation and Evaluation after ICD therapy

Data Collection Requirement	Retention of Original Source Documentation
• Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable • Cardiac Medication Changes	Investigational Center
• Device Follow Up Report • Selected Episode Electrograms, as applicable • Device Settings Report • Settings Change Report • Arrhythmia log book	Printed Copy of all final reports retained at Investigational Center Save to USB for Investigational Site. Copy will be sent to sponsor, if applicable Upload USB into EDC system

For subjects remotely monitored on LATITUDE:

If the LATITUDE database shows an alert related to a treated episode and/or the subject reports a treated episode, it will be at the Investigator Discretion, per their SOC if they want to bring the subject in to be seen for an unscheduled visit. The treated episode will be collected via the LATITUDE system and uploaded into the study database by the LATITUDE BSC team.

If the center does not bring the patient in for a treated episode as their standard of care practice, the coordinating Investigational center needs to call the patient to evaluate:

- Cardiac medication changes
- Reportable adverse events
- Device deficiencies

11.9. *Device reprogramming outside of Investigational Plan*

Once a subject is programmed to their respective randomized arm, every effort will be made to keep the subject's device programmed per the required programming in this protocol. Device reprogramming can be made if clinically indicated based on safety concerns. All device reprogramming changes, including the reason for change, must be recorded as a protocol deviation and the clinical circumstances must be documented as SAE or a device related adverse event, as applicable. After reprogramming to device settings outside of the required programming per protocol, subjects will remain in the assigned treatment arm until the end of the study to follow the methodology of intention-to-treat (ITT). Deviated programming doesn't qualify as reason for study withdrawal, and subjects will continue to be followed per the investigational plan.

11.10. *Study Completion*

The study will conclude after the earliest of one of following occurrences: (1) one arm is determined to be superior at one of the three interim analyses (per Section 12.3.1), or (2) a sufficient number of shock episodes have occurred to provide the desired power. It is expected that the last enrolled patient will be followed for approximately 18 months and the first enrolled patient will be followed for approximately 60 months. Sites will continue to follow subjects until notified of follow-up completion. Sites will be notified when subject follow-up is complete for the study.

11.11. *Source Documents*

Original source documents are required to be retained at the center. Where copies of the original source document as well as printouts of original electronic source documents are

retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

NOTE: If thermal paper from the device programmer was used for source documentation, photocopies or printed pdfs should be prepared and kept for source documentation.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint - Time-to-First All-Cause Shock

The incidence of all-cause shocks in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.

12.1.1.1. Hypotheses

The hazard ratio of all-cause shocks will be used to evaluate the equivalence of shocks only programming and standard therapy. A relative equivalence margin of 35% in each direction will be employed. The following hypotheses will be used.

H_0: Hazard Ratio ≤ 0.65 or Hazard Ratio $\geq (1/0.65)$

H_A: $0.65 <$ Hazard Ratio $< (1/0.65)$

12.1.1.2. Sample Size

A total of 2600 subjects – 1300 per group – will be required to sufficiently power the primary endpoint. The sample size of 2600 subjects will provide the number of primary endpoint events necessary to power the Primary Endpoint. Two assumption scenarios were considered to determine the required sample size.

	Scenario 1	**Scenario 2**
Expected all-cause shock rate in each group	6%	7%
Alpha	5%	5%
Power	90%	90%
Equivalence Margin	(0.65 – [1/0.65]) = (0.65 – 1.54)	(0.65 – [1/0.65]) = (0.65 – 1.54)
Attrition at 18 months	10%	10%
Enrollment Period	42 months	42 months
Follow-up Period	First Patient: 60 months Final Patient: 18 months	First Patient: 54 months Final Patient: 12 months
Maximum Trial Duration	60 months	54 months

12.1.1.3. Statistical Methods

All implanted and randomized subjects will contribute to the analysis of the Primary Endpoint. Cox proportional hazards modeling will be performed, with time-to-first shock therapy episode used as the outcome and programming scheme used as the covariate in the model. Traditional therapy will be considered the reference group in the analysis. Each subject's first shock therapy episode will contribute to the analysis. Subjects without a shock therapy episode will be censored at their date of death, withdrawal, study exit or on the date of the data snapshot, whichever occurs first. From the Cox model, the hazard ratio and corresponding confidence interval for programming scheme will be calculated. If the confidence interval for the hazard ratio is fully contained within the equivalence region – between 0.65 and 1.54 – equivalence of shocks only and standard programming will be concluded.

If equivalency cannot be established, further testing for superiority will be performed without need for a multiplicity adjustment to the significance level of the test beyond the adjustment necessary to accommodate the interim superiority tests. This additional testing is possible because the equivalence test is comprised of two separate one-sided non-inferiority tests. If non-inferiority is established for only one of the two one-sided non-inferiority tests, superiority can further be tested, per gating methodology.

The following table outlines the possible results and conclusions that can be drawn from the Primary Endpoint analysis.

Result of Lower Confidence Limit of Confidence Interval	Result of Upper Confidence Limit of Confidence Interval	Conclusion
>0.65	<1.54	Equivalence of shocks only to standard therapy
≤0.65	≥1 and <1.54	Non-inferiority of shocks only to standard therapy
<0.65	<1	Superiority of shocks only to standard therapy
≤1 and >0.65	>1.54	Non-inferiority of standard therapy to shocks only
>1	>1.54	Superiority of standard therapy to shocks only

12.1.2. Secondary Endpoint 1 - Time-to-First All-Cause Shock or Death from Any Cause

The incidence of all-cause shocks or death in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.

12.1.2.1. Hypotheses

The hazard ratio of all-cause shocks or death will be used to evaluate the equivalence of shocks only programming and standard therapy. A relative equivalence margin of 35% in each direction will be employed. The following hypotheses will be used.

H0: Hazard Ratio ≤ 0.65 or Hazard Ratio $\geq (1/0.65)$

HA: $0.65 <$ Hazard Ratio $< (1/0.65)$

12.1.2.2. Statistical Methods

All implanted and randomized subjects will contribute to the analysis of Secondary Endpoint 1. Cox proportional hazards modeling will be performed, with time-to-first shock therapy episode or death used as the outcome and programming scheme used as the covariate in the model. Traditional therapy will be considered the reference group in the analysis. Each subject's death or first shock therapy episode will contribute to the analysis. Subjects that survived the follow-up duration without a shock therapy episode will be censored at their date of withdrawal, study exit or on the date of the data snapshot, whichever occurs first. From the Cox model, the hazard ratio and corresponding confidence interval for programming scheme will be calculated. If the confidence interval for the hazard ratio is fully contained within the equivalence region – between 0.65 and 1.54 – equivalence of shocks only and standard programming will be concluded. In the event that equivalency cannot be established, superiority testing will be performed, employing similar methodology to that described for the Primary Endpoint.

12.1.3. Secondary Endpoint 2 – Time-to-Death from Any Cause

Hazard of death from any cause in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.

12.1.3.1. Hypotheses

The hazard ratio of death will be used to evaluate the equivalence of shocks only programming and standard therapy. A relative equivalence margin of 35% in each direction will be employed. The following hypotheses will be used.

H_0: Hazard Ratio ≤ 0.65 or Hazard Ratio $\geq (1/0.65)$

H_A: 0.65 < Hazard Ratio < (1/0.65)

12.1.3.2. Statistical Methods

All implanted and randomized subjects will contribute to the analysis of Secondary Endpoint 2. Cox proportional hazards modeling will be performed, with time-to- death used as the outcome and programming scheme used as the covariate in the model. Traditional therapy will be considered the reference group in the analysis. Each subject's death will contribute to the analysis. Subjects that survived the follow-up duration will be censored at their date of withdrawal, study exit or on the date of the data snapshot, whichever occurs first. From the Cox model, the hazard ratio and corresponding confidence interval for programming scheme will be calculated. If the confidence interval for the hazard ratio is fully contained within the equivalence region – between 0.65 and 1.54 – equivalence of shocks only and standard programming will be concluded. In the event that equivalency cannot be established, superiority testing will be performed, employing similar methodology to that described for the Primary Endpoint.

12.1.4. Secondary Endpoint 3 – Time-to-First Appropriate Shock

The incidence of appropriate shocks in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.

12.1.4.1. Hypotheses

The hazard ratio of appropriate shocks will be used to evaluate the equivalence of shocks only programming and standard therapy. A relative equivalence margin of 35% in each direction will be employed. The following hypotheses will be used.

H_0: Hazard Ratio ≤ 0.65 or Hazard Ratio ≥ (1/0.65)

H_A: 0.65 < Hazard Ratio < (1/0.65)

12.1.4.2. Statistical Methods

All implanted and randomized subjects will contribute to the analysis of Secondary Endpoint 3. Cox proportional hazards modeling will be performed, with time-to-first appropriate shock therapy episode used as the outcome and programming scheme used as the covariate in the model. Traditional therapy will be considered the reference group in the analysis. Each subject's first appropriate shock therapy episode will contribute to the analysis. Subjects without an appropriate shock therapy episode will be censored at their date of death, withdrawal, study exit or on the date of the data snapshot, whichever occurs first. From the Cox model, the hazard ratio and corresponding confidence interval for programming scheme will be calculated. If the confidence interval for the hazard ratio is fully contained within the equivalence region – between 0.65 and 1.54 – equivalence of shocks only and standard programming will be concluded. In the event that equivalency cannot be established, superiority testing will be performed, employing similar methodology to that described for the Primary Endpoint.

12.1.5. Secondary Endpoint 4 – Time-to-First Inappropriate Shock

The incidence of inappropriate shocks in subjects programmed with shocks only will be compared with subjects programmed to standard therapy (ATP and shock) to assess equivalency.

12.1.5.1. Hypotheses

The hazard ratio of inappropriate shocks will be used to evaluate the equivalence of shocks only programming and standard therapy. A relative equivalence margin of 35% in each direction will be employed. The following hypotheses will be used.

H_0: Hazard Ratio ≤ 0.65 or Hazard Ratio $\geq (1/0.65)$

H_A: $0.65 <$ Hazard Ratio $< (1/0.65)$

12.1.5.2. Statistical Methods

All implanted and randomized subjects will contribute to the analysis of Secondary Endpoint 4. Cox proportional hazards modeling will be performed, with time-to-first inappropriate shock therapy episode used as the outcome and programming scheme used as the covariate in the model. Traditional therapy will be considered the reference group in the analysis. Each subject's first inappropriate shock therapy episode will contribute to the analysis. Subjects without an inappropriate shock therapy episode will be censored at their date of death, withdrawal, study exit or on the date of the data snapshot, whichever occurs first. From the Cox model, the hazard ratio and corresponding confidence interval for programming scheme will be calculated. If the confidence interval for the hazard ratio is fully contained within the equivalence region – between 0.65 and 1.54 – equivalence of shocks only and standard programming will be concluded. In the event that equivalency cannot be established, superiority testing will be performed, employing similar methodology to that described for the Primary Endpoint.

12.1.6. Tertiary Objectives

12.1.6.1. Multivariate analyses

The purpose of this tertiary objective is to determine covariates associated with the use of ATP, bradycardia pacing, and the need for future CRT-D pacing therapy. The number of sustained VT episodes that occur in the monitor only zone and the percentage of patients that have these events will also be evaluated. Each outcome will be assessed separately, resulting in three separate multivariate Cox proportional hazards models. Covariates considered for inclusion in the final multivariate models include, but are not limited to, the characteristics listed in Section 12.3.2.

12.1.6.2. Latitude Alerts

The purpose of this tertiary objective is to (1) characterize the usage rates of HeartLogic among study patients, (2) characterize the alert rates among patients using HeartLogic, and (3) evaluate if usage and/or alerts are associated with changes in clinical therapy, the occurrence of adverse events, or other patient outcomes.

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

All primary and secondary endpoint analyses will be performed following intention-to-treat (ITT) methodology, in which each subject is analyzed per their intended (i.e., randomized) treatment assignment. An as-treated analysis may be performed as well, in which subjects would be analyzed per the treatment received and may be time-varying to accommodate cross-overs. A per-protocol analysis may also be performed, limited to the subjects that adhered to important protocol criteria. This list of criteria will be defined prior to analysis, but not necessarily prior to the start of the study, to allow for knowledge gained throughout the study execution to be reflected in the analysis.

12.2.2. Control of Systematic Error/Bias

Overall Type I error for the Primary Endpoint will not exceed 5%. Type I error will be split and managed for the interim superiority analyses by employing an O'Brien-Fleming-type error spending function. Superiority testing for each group will be performed with an overall Type I error of 2.5%, resulting in a total of 5% across both groups. As described in Section 12.1.1.3, in the event that equivalency is not established, Type I error will be controlled for the additional superiority test per gating methodology and will not require further multiplicity adjustments

To reduce the possible introduction of selection bias, subjects will be randomized to their treatment assignment. To reduce the possible introduction of observer bias, an objective primary outcome of device-recorded all-cause shocks will be evaluated. To reduce the possible introduction of classification bias for the secondary endpoints of appropriate and inappropriate shocks, shocks will be adjudicated by an independent electrogram adjudication core lab.

12.2.3. Number of Subjects per Investigative Site

No single site is to enroll more than 10% (260 patients) without the prior written approval from the sponsor or sponsor's delegated representative.

12.3. *Data Analyses*

12.3.1. Interim Analyses

Interim analyses will be performed to assess the superiority of shocks only or standard programming. Four analyses (three interim analyses and one final) are planned. The Type I error/alpha spending will be managed using an O'Brien-Fleming-type error spending function. The following alpha will be allocated for each analysis.

Analysis Number	Information Proportion at Time of Analysis	Cumulative Type I Error (Alpha) Spending	Significance Level Used for Analysis*
1	0.25	0.00001	0.00000736681
2	0.50	0.00153	0.00152000000
3	0.75	0.00965	0.00916000000
4	1.00	0.02500	0.02200000000

If P-value is less than specified significance level, superiority will be determined.

12.3.2. Subgroup Analyses

Analyses will be performed to assess whether significant interactions exist between randomization group and various baseline characteristics. Analyses will evaluate, but are not limited to, the following baseline characteristics and their corresponding subgroups.

Characteristic	Subgroup 1	Subgroup 2
Age	≥ 65	< 65
Gender	Female	Male
History of Atrial Fibrillation	AF	No AF
Ischemic Status	Ischemic	Non-Ischemic
Diabetes	Diabetic	Non-diabetic

Regardless of the results of the interaction test for each characteristic, analyses of each subgroup will be performed. Analyses will be conducted for the Primary Endpoint and all Secondary Endpoints.

12.3.3. Justification of Pooling

The study will be conducted globally. A Cox proportional hazards model for the Primary Endpoint will be performed, evaluating geography (e.g., continent) as a covariate in the model, to assess the poolability of the patients from different geographies.

12.3.4. Changes to Planned Analyses

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

13. Data Management

13.1. *Data Collection, Processing, and Review*

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

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

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

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

13.2. *Data Retention*

The Investigator or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an

individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Core Laboratories*

The Electrogram and Device Interrogation Core Laboratory will review interrogation data to determine primary endpoints that occur in APPRAISE ATP. Their decisions are based on independent physician review of the data from device interrogation. Responsibilities, qualifications, membership, and committee procedures are outlined in the EGM Adjudication Charter. Separate instructions regarding the core lab charter will be provided.

14. Amendments

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

15. Deviations

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

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

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

16. Compliance

16.1. *Statement of Compliance*

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

16.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.

- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.

- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.2.1. Delegation of Responsibility

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

16.3. *Institutional Review Board/ Ethics Committee*

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

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

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

16.4. *Sponsor Responsibilities*

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

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Role of Boston Scientific Representatives

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

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

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

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

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

Boston Scientific personnel will not do the following.

- Practice medicine

- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

16.5. *Insurance*

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

17. Monitoring

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

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

18. Potential Risks and Benefits

18.1. *Anticipated Adverse Events*

Subjects participating in this study are subject to the same risks shared by all patients undergoing implantation of a TV-ICD system. Based on the literature and on pulse generator implant experience, Table 18.1-1 includes an alphabetical list of the possible adverse events associated with implantation of a pulse generator and/or lead system.

Currently, there is no known incremental risk of adverse events coming from the trial. If there is a difference in outcomes between the arms, the subjects will be informed of the study outcome and may choose to have their programming to the most suitable at the conclusion of the study.

Table 18.1-1: Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System Implants

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Air embolism	Lead dislodgment
Allergic reaction	Lead fracture
Bleeding	Lead insulation breakage or abrasion
Bradycardia	Lead perforation
Cardiac tamponade	Lead tip deformation and / or breakage
Chronic nerve damage	Local tissue reaction
Component failure	Loss of capture
Conductor coil fracture	Myocardial Infarction (MI)
Death	Myocardial necrosis
Elevated thresholds	Myocardial trauma (e.g., tissue damage, valve damage)
Erosion	Myopotential sensing
Excessive fibrotic tissue growth	Oversensing / undersensing
Extracardiac stimulation (muscle/ nerve stimulation)	Pacemaker-mediated tachycardia (PMT) (Applies to dual-chamber devices only.)
Failure to convert an induced arrhythmia	Pericardial rub, effusion
Fluid accumulation	Pneumothorax
Foreign body rejection phenomena	Pulse generator migration
Formation of hematomas or seromas	Shunting current during defibrillation with internal or external paddles
Heart block	Syncope
Heart failure following chronic RV apical pacing	Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
Inability to defibrillate or pace	Thrombus, thromboemboli
Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)	Valve damage
Incisional pain	Vasovagal response
Incomplete lead connection with pulse generator	Venous occlusion
Infection including endocarditis	Venous trauma (e.g. perforation, dissection, erosion)
Insulating myocardium during defibrillation with internal or external paddles	Worsening heart failure

From the DYNAGEN, INOGEN, ORIGEN, INCEPTA, ENERGEN, PUNCTUA, TELIGEN Physician's Technical Manual Oct 01, 2015; Part Number: 359403-002

Patients may develop psychological intolerance to a pulse generator system and may experience the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost

- Imagined shocking
- Fear of device malfunction

An addition potential risk has been identified for this study:

- Delayed therapy delivery

18.2. *Anticipated Adverse Device Effects*

Adverse Device Effects that are part of the listing in the previous18.1 section are to be considered Anticipated Device Effects.

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

Improved ICD programming to high rates and extended duration delays has been demonstrated to be safe and effective in the MADIT RIT[3] clinical trial, and no incremental risks are anticipated for this study. The programming used in APPRAISE ATP aligns with the current 2015 HRS Consensus guidelines – Manufacturer Specific Translation of the HRS Consensus[4]. However, if a programming arm does not seem suitable for the individual patient, clinical judgment must be used in programming the devices after a spontaneous event has occurred.

Participation in this clinical trial occurs post device implantation, and Investigators have already chosen to implant a subject with an ICD for primary prevention indications. For women of childbearing potential, it will be at the Investigators discretion to enroll this population into the trial. No incremental risks are anticipated for this study to women of childbearing potential.

18.4. *Risk Minimization Actions*

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

18.5. *Anticipated Benefits*

There may be no benefit to the subject. However, medical science and future patients may benefit from their participation in this clinical study. If there is a superior or inferior arm, the subjects can be programmed at the conclusion of the study to the best programming suitable to their needs.

18.6. *Risk to Benefit Rationale*

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

The recently published Expert Consensus Statement on Optimal Implantable Cardioverter Programming and Testing[15] includes information on optimal ICD programming for primary prevention patients, and the purpose is to provide evidence based expert guidance. The detection duration and rate programming in APPRAISE ATP is aligned with the recommendation for primary prevention ICD per this Consensus Statement.

19. Safety Reporting

19.1. *Reportable Events by investigational site to Boston Scientific*

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

- All Serious Adverse Events
- All Device Related Adverse Events
    - PMT does not have to be reported unless the patient is symptomatic and it is true PMT. Document if there was a change in programming related to the PMT.
    - Bradycardia only to be reported if the subject is symptomatic to the bradycardia
- All Serious Adverse Device Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All Arrhythmic Related Events:
    - Any treated or untreated ventricular event if not already documented as:
        - A sustained ventricular episode in the monitoring zone
        - SAE
        - A new onset of an atrial event not reported in the Medical History
            - ATR episodes do not need to be reported if it is a response to a known and/or previously reported atrial arrhythmia
- Syncope

  - Including reports of near syncope, which could include but not limited to symptoms of dizziness, lightheadedness, fainting

- For subjects with a HeartLogic Alert, any change in heart failure therapy which requires IV treatment should be reported as an AE.
- New findings/updates in relation to already reported events

For Event reporting the medical diagnosis must be reported. In case the diagnosis is not available, individual symptoms can be reported to fulfill reporting timelines. If a diagnosis becomes available at a later stage, it must be added to the reported event.

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

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reportable as AEs unless there is an increase in severity of frequency during the course of the investigation. For centers in Austria cancer must always be reported as a Serious Adverse Event. Death events itself are not be recorded as an SAE, but must be reflected as an outcome of ONE (1) specific SAE/ SADE or USADE (see Table 20.2-1 for Event definitions).

Refer to Section 18 for the known risks associated with the study device(s).

19.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3 for clarification purposes. Adverse events to be reported per section 19.1.

Table 19.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved.

Table 19.2-1: Safety Definitions

Term	Definition
	NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject as defined by either: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization , or o in medical or surgical intervention to prevent life-threatening illness o injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Table 19.2-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3	**NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

19.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 19.3-1:

Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error;

Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in 19.4-1

Adverse events must always be reported through the EDC system for APPRAISE ATP. However, in the case of any issues where alternative method of reporting is necessary (i.e. the EDC system is not available), please report the adverse event to Boston Scientific by sending the Event Notification Form via email to the following email address:

APPRAISEATPSafety@bsci.com

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies**** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations, with the exception of deaths (to be reported within 3 calendar days of center notification.) • For Austria: within 2 business days of first becoming aware of the event. • Reporting required through the end of the study

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

Event Classification	**Communication Method**	**Communication Timeline post-market studies**** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)

19.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction would be recorded as an adverse event on the appropriate eCRF.

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

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

Boston Scientific is responsible for reporting adverse event information to all participating Principal Investigators, IRB/ECs, and regulatory authorities, as required by local/regional regulations. The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

19.7. *Subject Death Reporting*

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

A detailed narrative (death letter), may be requested at BSC discretion that provides detailed information describing the circumstances surrounding the death. A death narrative in the local

language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

• Date and time of death;

• Place death occurred;

• Immediate cause of death;

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

• Whether or not the death was witnessed;

• Whether the subject had worsening heart failure;

• Any other circumstances surrounding the death;

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

• Investigator or co-Investigator signature and date.

Other Source documents maybe requested at BSC.

20. Informed Consent

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

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

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

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

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

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

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

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

21. Committees

21.1. *Data Monitoring Committee*

An Independent Data Monitoring Committee (DMC) will meet periodically, or as needed, to review the results of the trial and to evaluate any safety issues that may arise during the course of the study. The DMC will include leading experts in Electrophysiology, who are not participating in the APPRAISE ATP study, and have no affiliation with BSC. The DMC will inform the study Principal Investigator on any safety concerns and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

21.2. *Steering Committee*

The Steering Committee is independent of Boston Scientific RM and is responsible for the overall conduct of the study with regard to protocol development, study progress, subject safety, and overall data quality and integrity. A list of the Steering Committee Members is provided on page 3 of this protocol.

22. Suspension or Termination

22.1. *Premature Termination of the Study*

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

22.2. *Criteria for Premature Termination of the Study*

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

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

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

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

22.4. *Requirements for Documentation and Subject Follow-up*

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

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

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

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

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

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, the IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed according to the standard of care. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

23. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study

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

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

24. Reimbursement and Compensation for Subjects

24.1. *Compensation for Subject's Health Injury*

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

25. Bibliography

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[15]Bruce L. Wilkoff, Laurent Fauchier, Martin K. Stiles, et al: 2015 HRS/EHRA/APHRS/SOLAECE Expert Consensus Statement on Optimal Implantable Cardioverter-Defibrillator Programming and Testing, Europace (2015) euv411 DOI: http://dx.doi.org/10.1093/europace/euv411 First published online: 19 November 2015 euv411

[16] The manufacturer specific programming settings/choices are based on a compilation of clinical expertise and clinical trial data as reported in the 2015 Consensus Statement On Optimal ICD Programming and Testing
http://web.hrsonline.org/Health-Policy/Clinical-Documents/Appendix-B-Manufacturer-Specific-Translation-of-Recommendations.pdf

26. Abbreviations

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
ATP	Anti-tachycardia pacing
bpm	beats per minute
BSC	Boston Scientific
CFR	Code of Federal Regulations
CRF	Case Report Form
CRT-D	Cardiac Resynchronization Therapy –Defibrillator
eCRF	Electronic Case Report Form
EU	European Union
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EGM	Electrogram
FCC	Federal Communications Commission
GCP	Good Clinical Practice
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IRB	Institutional Review Board
ITT	Intention-to-Treat
J	Joules
LAT	LATITUDE
LVEF	Left Ventricular Ejection Fraction
ms	Millisecond
N/A	Not Applicable
NNT	Number Needed to Treat
NR	Not Required
NYHA	New York Heart Association
OUS	Outside the United States
PG	Pulse Generator

ppm	pulses per minute
RM	Rhythm Management
SAS	Statistical Analysis System
SOC	Standard of Care
Spontaneous Episode	Any arrhythmia that is stored within the BSC transvenous ICD PG
TV-ICD	Transvenous ICD
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

27. Appendices

In addition, the definitions and classifications are applicable to RM. BSC reviews and codes all reported events.	
Clinical Observation *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	A clinical observation is a clinical event that did not result in invasive intervention, injury, or death, and is not an unanticipated adverse event. Corrective actions were simple adjustments such as reprogramming of the pulse generator or antibiotic treatment of a pocket infection
Clinical Complication *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	A clinical complication is a clinical event that required an invasive intervention, injury, or death (e.g., surgical evacuation of a hematoma, lead dislodgment requiring lead repositioning, generator replacement, loss or abandonment of therapy).
Type I *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to the investigational device or therapies.

Type II *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to protocol or procedures. Specifically related to protocol testing that is not patient standard of care.
Type III *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Not related to the investigational device(s), system component(s), or labeling, but would not have occurred in the absence of the investigational device(s) and/or system component(s). This includes clinical events related to commercially released devices that are used in conjunction with investigational device(s) or protocol procedures.
Type IV *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to a change in patient's condition.
Type V *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Comments Only. On occasion, comments were inadvertently entered in the adverse event text field of the case report form (CRF). Comments identified by the CRF reviewer were assigned a Type V code and not included in this report.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board