Understanding Outcomes with the EMBLEM™ S-ICD in Primary Prevention Patients with Low Ejection Fraction

UNTOUCHED

CLINICAL PROTOCOL

Reference Number C1851

Sponsored By

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Investigational Sites	An updated list of site Principal Investigators, Investigational Sites, and Institutions, is kept separately from the protocol.
Vendors	A list of vendors involved in the trial is maintained by the sponsor.

Original Release: 6. February 2015

Current Version: AC

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	6 February 2015	90702637 Rev./Ver. AE	NA	Original Release	NA
AB	24 February 2015	90702637 Rev./Ver. AE	1 Protocol Synopsis and 5 Objectives	Added secondary objective	To link secondary endpoint to objective of the study
			10.10 Source documents	If original source documents including, but not limited to, printouts of original electronic source documents are not retained, copies shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.	If original documents can still be retrieved at the site the statement is not required. Only in case source documents cannot be retrieved.
			19.Safety Reporting	Revised whole section	Align with BSC work instruction on Event coding/classification and maintenance
			Table 10.1	Added AE reporting requirement from enrollment on	AE reporting starts from enrollment on
			21. Clinical Events Committee	Committee membership will include experts with the necessary therapeutic area and subject matter expertise to adjudicate reported shock episodes	Clarify scope of Clinical Events Committee

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AC	10 February 2016	90702637 Rev./Ver. AF	All	Adapt protocol to new template	Changes in regulatory requirements and admin changes
			Contact Information, US Clinical Contact	Added [redacted] as US Clinical Contact	New Clinical Trial Manager joined study team
			Contact Information, Coordinating Principal Investigators	Added Dr. Michael Gold as Coordinating Principal Investigator	United States Principal Investigator joined the study
			Contact Information, Investigational Sites	Added: An updated list of site Principal Investigators, Investigational Sites, and Institutions, is kept separately from the protocol.	Site list will be kept separately from the protocol
			Contact Information, Vendors	Removed Labs from Role column Removed reference to NAMSA and added: A list of vendors involved in the trial is maintained by the sponsor.	Not applicable to this study Vendor information will documented separately.
			1 Protocol Synopsis, Study Objective(s)	Added: 'Inappropriate' to description of primary objective Corrected beats per minute acronym from bmp to bpm Changed definition of secondary objective to include additional	Primary Endpoint changed from assessment of All-Cause shocks to assessment of Inappropriate shocks Typo Secondary objective was added to assess the

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				secondary objective of assessment of All-Cause shocks: The secondary objectives are to assess the 18-month incidence of all-cause shocks and perioperative complications.	18-months incidence of All-Cause Shocks as planned in the initial protocol
			Throughout document	Replaced: EMBLEM S-ICD with EMBLEM™ S-ICD	Added product trademark
			1 Protocol Synopsis, Planned Number of Subjects	Changed number of subjects from minimum of 2015 to minimum of 1,100. Patients who do not undergo implant procedures will not count towards this number.	Subject enrollment minimum decreased to speed up overall study duration
			1 Protocol Synopsis, Primary Endpoint	Changed Shock Free Rate to Inappropriate Shock Free Rate Changed performance goal from 87.2 to 91.6%	Primary Endpoint changed from assessment of All-Cause shocks to assessment of Inappropriate shocks Performance goal modified; statistical goal explained in Section 11 Statistical Considerations
			1 Protocol Synopsis, Secondary Endpoint	Added new secondary objective for assessment of All-Cause shocks and changed performance goal from 87.2 to 85.8%: The All-Cause Shock Free Rate at 18 months compared to a	Assessment of All-Cause shocks moved from the primary endpoint in version AB to a secondary endpoint in version AC Performance goal modified; statistical goal explained in

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				performance goal of 85.8%	Section 11 Statistical Considerations.
			1 Protocol Synopsis, Additional Endpoints	Removed the following endpoint from list, as it is now the Primary Endpoint: Freedom from Inappropriate Shocks at 18 months	Primary Endpoint changed from assessment of All-Cause shocks to assessment of Inappropriate shocks
			1 Protocol Synopsis, Follow-up Schedule	Added comma and 'the' to the following: enrollment, implant, and pre-discharge visits, the scheduled in clinic follow-up visits	Minor changes for improved clarity
			1 Protocol Synopsis, Study Duration	The sentence: The duration of the study, from first enrollment to study closure, is expected to be approximately 78 months. Is replaced by: The duration of the study, from first enrollment to the last patient's final visit is expected to be approximately 51 months. Individual patients will be followed from enrollment until their 18 month follow-up visit.	Study duration was shortened so that data would be available sooner than planned in version AB. Added description of the length of time that individual subjects will be followed.
			1 Protocol Synopsis, Inclusion Criteria	Modified inclusion criteria	Replacement devices are no longer allowed. Only de novo EMBLEM implants can be enrolled to eliminate any potential replacement bias

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
					Removed unneeded reference to User Manual for screening ECG criteria, as well as reference to currently implanted S-ICDs Removed requirement of an ECG demonstrating sinus rhythm within 30 days of enrollment Added criteria requiring that the patient be willing and capable of complying with follow-up visits
			1 Protocol Synopsis, Exclusion Criteria	Modified exclusion criteria	Changed the VT/VF exclusion criteria to "Patient with a history of spontaneous sustained VT or VF" Patients with a previous S-ICD or a transvenous pulse generator cannot be enrolled Removed AF exclusion criteria, as all AF patients can be enrolled. Removed QRS width exclusion criteria; no restriction on QRS width Updated dialysis related criteria to now exclude patients received hemodialysis rather than dialysis

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
					Added exclusion for patients in a concurrent study without prior approval from BSC Changed CRT indication to patients eligible and scheduled for CRT implant Added: Medical status (e.g., hemodynamic conditions) of the patient doesn't allow programming devices with a conditional shock zone at 200 bpm and a shock zone at 250 bpm, in the judgment of the implanting physician and/or per national or international guidelines
			1 Protocol Synopsis,	Removed 'Multiple Interventions During Index Procedure' section	This section was specific to device replacements being allowed in the study. Section removed as it is no longer applicable.
			1 Protocol Synopsis, Primary Statistical Hypothesis	Updated section to reflect new inappropriate shock primary endpoint and the all-cause shock endpoint moving to a secondary endpoint	Primary and Secondary endpoints being updated as described above
			1 Protocol Synopsis, Sample Size Parameters	Decreased subject enrollment sample size and modified the power of the secondary effectiveness endpoint to 90% and additional subjects for the subgroup analysis of	Sample size, Secondary endpoint, and ability to enroll all AF patients, as described above

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				permanent atrial fibrillation.	
			1 Protocol Synopsis, Table footnote	Added footnote explaining that replacement devices were allowed in previous version of the protocol.	See inclusion criteria change above
			1 Protocol Synopsis, Data Collection Schedule	Copied Data collection Schedule from section 10.1 Data Collection into the protocol synopsis.	To emphasize this information earlier in the document
			Table of Contents	Updated section header names, numbers, and page numbers	Necessary after protocol revisions
			Section 4 Device Description	Added statement that the integrated screening tool can be used, once available.	Future EMBLEM devices are planned to include an integrated screening tool that will replace existing manual process. This integrated tool can be used.
			Section 4.2 EMBLEM S-ICD Subcutaneous Electrode	Removed duplicate sentence regarding future generations of electrodes.	Duplicate
			Section 4.4 EMBLEM S-ICD Programmer	Removed 'and/or keyboard' regarding user input.	The programmer does not have a keyboard so this is unnecessary.
			Section 5 Objectives	Added 'inappropriate' to primary objective description	Primary Endpoint changed from assessment of All-Cause shocks to assessment of Inappropriate shocks

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				Changed acronym from bmp to bpm Updated secondary objective description to include All-Cause Shocks	Fixed incorrect acronym for beats per minute. Secondary objective was added to assess the 18-months incidence of All-Cause Shocks
			Section 6 Study Endpoints and Analysis	Changed header from Pre-specified Endpoints and Analyses to Study Endpoints and Analyses Added 'inappropriate' to primary objective description Changed performance goal from 87.2 to 91.6% Updated secondary objective description to include All-Cause Shocks Removed the following endpoint from list, as it is now the Primary Endpoint: Freedom from Inappropriate Shocks at 18 months	Clarification change Primary Endpoint changed from assessment of All-Cause shocks to assessment of Inappropriate shocks Changed performance goal Secondary objective was added to assess the 18-months incidence of All-Cause Shocks This is now the primary endpoint, not part of the additional analyses
			Section 7 Design	Added de novo and removed reference to replacements	Replacement devices can no longer be enrolled
			Section 7.1 Scale and Duration Page 26	Changed enrollment minimum to 1,100 Modified duration information.	Subject minimum changed from 2,015 to 1,100

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
					Study duration decreased
			Figure 7-1 UNTOUCHED Study Design	Added a box to describe 30-day follow-up for enrolled patients that are not successfully implanted Added box for Pre-Discharge visit	Info not included in figure in previous version
			Section 8.1 Study Population and Eligibility	Changed "low" to "reduced"	To better define the ejection fraction population
			Section 8.2 Clinical Inclusion Criteria	Modified Inclusion criteria as described above	Inclusion criteria changed
			Section 8.2 Clinical Exclusion Criteria	Modified Exclusion criteria as described above	Exclusion criteria changed
			Section 9.1 Point of Enrollment	Patients consented but who finally will not undergo an implant procedure, regardless whether successful or not, will not be counted towards the minimum required sample size.	Avoid screening failures and patients who finally change their mind before implant
			Section 9.2 Withdrawal	Added statement regarding data being collected up to the point of subject withdrawal and no additional data will be collected after withdrawal.	Adding as clarification.
			Section 9.3 Loss to Follow-up	Added information regarding 3 mandatory attempts being required to follow-up with	Adding as clarification

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				patients that are lost to follow-up	
			Section 9.4 Subject Status and Classification	Enrolled patients that were found to be screening failures, will be handled like intent. Patients shall be withdrawn and End of Study Form completed to document. Intent patients will not count towards the enrollment ceiling.	Logistical reason in database
			Section 9.5 Enrollment Controls	Changed enrollment minimum to 1,100 and single site maximum to 110 patients	Subject minimum changed from 2,015 to 1,100. Avoid center bias
			Section 10.1 Data Collection	Changed: Reportable adverse clinical event To: Reportable adverse event Changed: Device malfunction To: Device deficiency	For consistency throughout document
			Table 10-1 Data Collection Schedule	Added 'from implant' to the Semi-Annual Follow-up windows in the header Added * to Protocol Deviations row for the Enrollment Visit column	For clarity and consistency Deviations that occur in association with the enrollment visit must be collected
			Section 10.2 Study Candidate Screening	Changed: Procedure may be de novo To:	Only de novo implants can be enrolled. Ability to enroll replacement devices was removed.

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				Procedure must be a de novo Removed reference to enrolling replacement devices	
			Section 10.3 Informed Consent and Enrollment	Added 'data entry' to first paragraph Deleted duplicate sentence in second paragraph regarding patients being considered enrolled once the consent form has been signed.	To clarify that no data entry can be performed prior to consenting the patient. This statement is included in the first paragraph of this section.
			Table 10-2 Enrollment Data Collection	Deleted de novo and replacement ICD bullet for the Screening ECG row	Not needed as only de novo devices can be enrolled in the study so this clarification is no longer needed
			Section 10.4 Implant Procedure and Data Collection	Added de novo and removed reference to replacement devices.	Only de novo devices can be enrolled in the study
			Table 10-3 Implant Data Collection	Changed: Episode strips To: Episode Induction S-ECG Report	Modified this to match the report name
			Section 10.4.1 Conversion Testing	Modified to clarify that all conversion tests will be collected. Formerly only those between the time of implant and pre-discharge were collected.	Will be collecting all induction tests to thoroughly evaluate adverse events and to fully understand extent of system testing that was performed

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
			Section 10.7 Additional Follow-up Visits	Updated: Hospitalizations should be recorded To: Hospitalizations shall be recorded Updated first bullet from: Spontaneous episodes To: Treated spontaneous episodes	These are required to be recorded if they meet the protocol definition of an additional follow-up visit For consistency throughout document, as only treated episodes qualify as an additional visit
			Section 11	Statistical Considerations Changes to primary and secondary endpoints, sample size, hypotheses, methods, pooling analysis	Changes to primary and secondary endpoints, decreased sample size, and inclusion of all AF patients.
			Section 12.2 Data retention	Added: Changed: The Investigator or Investigational site To: The Investigator or his/her designee or the Investigational site Added statement that documents must be retained for at least 2 years after study is closed	Adding because it was not included in previous version
			Section 15 Device/Equipment Accountability	Added: Device stickers (model/serial number) should be attached to the implant source documentation, if available.	To avoid transcription errors

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
			Section 16.3.1 Delegation of Responsibility	Added: Delegated tasks must be appropriately documented in the Site Signature Responsibility Log. Members of the study team must not perform tasks delegated to them by the Investigator until completion of all pertinent trainings.	Reminder to make sure delegated personnel are appropriately trained.
			Section 16.5.1 Role of Boston Scientific Representatives	Removed: • Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements And: Pacing System Analyzer	Not applicable to SICD
			Section 16.6 Insurance	Section added	Clarification that Boston Scientific will provide study insurance as required
			Section 17 Monitoring	Added Investigator has adequate oversight of trial conduct	Check study oversight
			Section 17 Monitoring	Changed important to expected for availability of site personnel during monitoring visit	To allow discussion about findings
			Section 18.2 Anticipated Adverse Device Effects	Changed to: Adverse Device Effects that are part of the listing in the previous paragraph 18.1 are to be considered Anticipated Adverse Device Effects.	Clarification

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
			Section 18.3 Risks associated with Participation in the Clinical Study	Changed to: The UNTOUCHED study includes the requirement to program devices with a conditional shock zone at 200 bpm and a shock zone at 250 bpm. These values are within the approved ranges of programmable settings and are in the range of the Tachycardia Dectection Programming Recommendations[11] and also reported in the literature[10]. The risks related to S-ICD therapy are the ones expected for the study population and have been listed under 18.1 Anticipated adverse events. No specific risks in addition to those mentioned in the listing are to be expected with participation in the UNTOUCHED study.	Data from Pooled Analysis and guidelines in consensus statement from societies.
			18.6. Risk to Benefit Rationale	Changed this section to reflect the current standard of practice as documented in literature	Consensus statement on optimal Implantable Cardioverter Defibrillator Programming and results from Pooled analysis on S-ICD studies
			19 Safety Reporting	Changed to: Only events as described below are reportable. For the purpose of this study the EMBLEM™ S-ICD System will be referred to as the study device. Reporting starts from the date of	Clarification

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				informed consent. Refer to Section 18 for the known risks associated with the study device(s). All device and/or procedure related adverse events regardless whether considered serious or not	
			Table 19-1: Event Definitions	Definitions updated according to new MEDDEV guidelines. Definition added for UADE Unanticipated Adverse Device Effect	Changes in regulatory requirements
			Table 19-2_Criteria for Assessing Relationship of Study Device to Adverse Event	Levels of relationship added: not related, unlikely related, Possibly related, Probably related and Causal Relationship with guidance	Changes in regulatory requirements.
			19.2 Investigator Reporting Requirements	Reworded	Clarification
			Table 19-3: Investigator Reporting Requirements	Added Timeline for reporting of UADEs/USADEs	Changes in regulatory requirements
			20 Informed Consent	Removed option of legally authorized representative in whole section	Not allowed per inclusion/exclusion criteria.
			21.1 Clinical Events Committee	Added clarification that the CEC will be adjudicating all shocks in an episode, and will classify each shock as appropriate or inappropriate.	Clarification
			25 Bibliography	Added reference to pooled data analysis and	No information affecting study

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				consensus statement for optimal ICD programming	
			26.2 Definitions	Definition added for inappropriate shocks	Clarification

1 Protocol Synopsis

Understanding Outcomes with the EMBLEM™ S-ICD in Primary Prevention Patients with Low Ejection Fraction (UNTOUCHED)	
Study Objective(s)	The primary objective is to assess the 18-month incidence of inappropriate shocks in subjects implanted with the EMBLEM Subcutaneous Implantable Defibrillator (S-ICD) programmed with zone cutoffs at 200 bpm and 250 bpm and: - an indication for implantation of a defibrillator for primary prevention of sudden cardiac death; - a left ventricular ejection fraction $\leq 35\%$. The 18-month incidence rate will be compared to an *Objective Performance Criteria* derived from transvenous ICDs programmed to minimize shocks in the MADIT RIT study. The secondary objectives are to assess the 18-month incidence of all-cause shocks and perioperative complications. Device and procedure related complications at 6 months and implant success rate at 3 months will be assessed to fulfill Post Market Clinical Follow-up (PMCF) requirements.
Planned Indication(s) for Use	The EMBLEM™ S-ICD System will be used within the current labeled indications. The EMBLEM™ S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.
Test Device	The EMBLEM Subcutaneous Implantable Defibrillator family (EMBLEM™ S-ICD). Future generations of the BSC subcutaneous defibrillators approved by the appropriate regulatory bodies may be included in the study.
Study Design	The UNTOUCHED Study is a global, multi-site, prospective, non-randomized study that will enroll subjects eligible for implantation with an EMBLEM™ S-ICD System and who also have: - an indication for primary prevention of sudden cardiac death; and - a left ventricular ejection fraction $\leq 35\%$.

Understanding Outcomes with the EMBLEM™ S-ICD in Primary Prevention Patients with Low Ejection Fraction (UNTOUCHED)	
	Devices will be programmed with zone cut-offs at 200 bpm (*Conditional Shock Zone*) and 250 bpm (*Shock Zone*). Subjects will be followed semi-annually according to standard of care for a minimum of 18 months post implant.
Planned Number of Subjects	A minimum of 1,100 patients will be enrolled. Investigational sites will be notified to cease enrolling subjects when at least 1,100 subjects have been entered in the database and an implant procedure was performed regardless whether successful or not. Patients consented but who finally will not undergo an implant procedure will not count towards the 1100 patients. Patients already consented at time of notification shall still be entered in the database and followed per study protocol.
Planned Number of Centers / Regions	Up to 200 sites in Asia / Pacific, Europe, Middle East, North America and South America.
Primary Endpoint	The primary endpoint is the Inappropriate Shock Free Rate at 18 months compared to a performance goal of 91.6%.
Secondary Endpoints	The secondary endpoints are: - The All-Cause Shock Free Rate at 18 months compared to a performance goal of 85.8% - Freedom from System and Procedure Related Complications at 30 days compared to a performance goal of 93.8%.
Post Market Clinical Follow-Up (PMCF) Endpoint	The Post Market Clinical Follow-up (PMCF) endpoint is Freedom from System and Procedure Related Complications at 6 months compared to a performance goal of 85%. Additionally, the 3-month implant success rate will be documented.
Additional Endpoints	• Freedom from Appropriate Shocks at 18 months • All-cause mortality • Syncope related to VT/VF episodes • Implantation of a concomitant pacemaker • Explants and causes

Understanding Outcomes with the EMBLEM™ S-ICD in Primary Prevention Patients with Low Ejection Fraction (UNTOUCHED)	
Method of Assigning Patients to Treatment	Investigators are responsible for screening patients who are candidates for an EMBLEM™ S-ICD system. Patients meeting the inclusion criteria and not meeting the exclusion criteria below shall be considered for enrollment in the UNTOUCHED study. Patients are considered enrolled in the study once the consent form has been signed.
Follow-up Schedule	After the enrollment, implant, and pre-discharge visits, the scheduled in clinic follow-up visits are to be performed at 180 day intervals from the implant date (i.e., 180-240 days, 360-420 days and 540-600 days post implant) in order to capture new (not previously reported): • Spontaneous episodes; • Reportable adverse events; • Programming changes; • Device deficiencies. Subject participation will end after a follow-up visit has been recorded at least 540 days after the index implant procedure.
Study Duration	The duration of the study, from first enrollment to the last patient's final visit is expected to be approximately 51 months. Individual patients will be followed from enrollment until their 18 month follow-up visit.
Inclusion Criteria	• Patient with ischemic or non-ischemic heart disease who meets current guidelines for ICD therapy and intends to undergo a de novo implant procedure for an EMBLEM™ S-ICD (or newer generation BSC S-ICD) • Left ventricular ejection fraction $\leq 35\%$ • A passing EMBLEM™ S-ICD (or newer generation BSC S-ICD) screening ECG • Patient ≥ 21 years of age willing and capable of giving informed consent • Patient willing and capable of complying with follow-up visits
Exclusion Criteria	• Patient with a history of spontaneous sustained VT or VF • Patient with bradycardia pacing indication • Patient eligible and scheduled for cardiac resynchronization implant

Understanding Outcomes with the EMBLEM™ S-ICD in Primary Prevention Patients with Low Ejection Fraction (UNTOUCHED)	
	• Patient with a previous S-ICD or a previous transvenous pulse generator (pacemaker or defibrillator) • Patient in NYHA Class IV documented in the medical records within 90 days before enrollment • Patient with life expectancy shorter than 18 months due to any medical condition (e.g., cancer, uremia, liver failure, etc…) • Patient receiving hemodialysis within 180 days before to enrollment • Patients unable to give consent in person, including patients unable to read or write • Patient who is known to be pregnant or plans to become pregnant over the course of the trial • Patient unwilling or unable to cooperate with the protocol • Participation in concurrent clinical study without prior approval from Boston Scientific • Medical status (e.g., hemodynamic conditions) of the patient doesn't allow programming devices with a conditional shock zone at 200 bpm and a shock zone at 250 bpm, in the judgment of the implanting physician and/or according to (inter) national guidelines

Statistical Methods	
Primary Statistical Hypothesis	**Primary Endpoint Hypothesis** The Inappropriate Shock Free Rate at 18 months exceeds the performance goal of 91.6%. **Secondary Endpoint Hypotheses** The All-Cause Shock Free Rate at 18 months exceeds the performance goal of 85.8% The System and Procedure Related Complication Free Rate at 1 month exceeds the performance goal of 93.8%. **PMCF Endpoint Hypothesis** The System and Procedure Related Complication Free Rate at 6 months exceeds the performance goal of 85.0%.
Statistical Test Methods	**Endpoint Analyses** The primary and secondary endpoints will be evaluated as proportions of subjects free from events based on the Kaplan-Meier method including the one-sided lower 95% confidence interval.[1] The Kaplan-Meier analysis will take into account the time from implant until the occurrence of an event or study exit (for subjects not experiencing an event). **Additional Pre-Specified Analyses** • Kaplan-Meier method for time to event analyses • Binomial estimates and exact confidence intervals for rates • Descriptive statistics such as mean, standard deviation, median, interquartile range, minimum and maximum for continuous data and frequency and percentage for discrete data. **Subgroup Analysis** Subgroup analyses of endpoints will be performed for key baseline/demographic characteristics. Continuous variables will be dichotomized for analysis. For time to event outcomes, the log-rank test will be utilized to compare the shapes of the Kaplan-Meier curves and tests whether or not the survival between groups are from the same distribution. **Reports**

[1] Peto method for standard error estimate

	At a minimum, annual progress reports will be provided throughout the duration of the study. A report will be prepared for submission to BSI on the first 200 enrolled subjects who undergo a de novo (i.e., not replacement of an S-ICD or TV-ICD*) implant procedure for the EMBLEM™ S-ICD System and have a follow-up visit at least 180 days after the index implant procedure. A final report will be prepared once the minimum number of patients have a follow-up visit at least 540 days after the index implant procedure.
Sample Size Parameters	[redacted]

*Replacement devices were allowed as part of the previous protocol version. For the BSI submission any replacement devices that were enrolled under that previous protocol version will not be included in this analysis.

Data Collection Schedule

	Enroll-ment Visit (No window)	Implant (No window)	Pre-Discharge (No window)	Semi-Annual Follow-up (Day 180-240; Day 360-420; Day 540-600)	Additional Follow-up (No Window)	Additional Implant (No Window)	End of Study (No Window)
Consent Date	X						
Baseline Characteristics	X						
Cardiovascular Medications	X						
Screening ECG	X						
Implant Details		X				X	

Data Collection Schedule

Follow-Up Details			X	X	X	X	X
S-ICD System Parameters		X	X	X	X	X	X
Reportable AEs / Device Deficiencies	*	*	*	*	*	*	*
Protocol Deviations	*	*	*	*	*	*	*
Spontaneous Episodes		*	*	*	*	*	*

X = required;
* = data entered only if the event occurred.

2 Table of Contents

2.1 *Table of Figures*

2.2 *Table of Tables*

3 Introduction

Implantable cardioverter defibrillator (ICD) therapy is highly effective for reducing mortality in patients with clinical markers for elevated risk for ventricular arrhythmias.[1-3] However, inappropriate shocks and unnecessary appropriate shocks remain an important side effect that can significantly affect an ICD recipient's quality of life[4,6] and may be deleterious to the myocardium.[7-9]

The MADIT RIT study[10] demonstrated that the incidence of inappropriate and unnecessary appropriate ICD therapy can be reduced in primary prevention patients through two different programming strategies: 1) High Rate Zone Cutoff, i.e., raising the lowest rate detection cutoff to 200 bpm and initiating treatment after 2.5 seconds (tested in treatment Arm B), and; 2) Delayed Therapy Initiation, i.e., increasing the time to therapy initiation to 60 seconds for arrhythmias detected between 170-199 bpm; 12.5 seconds between 200-249 bpm and 2.5 seconds above 250 bpm (tested in treatment Arm C). Both strategies effectively reduced the amount of ICD therapy delivered when compared to conventional programming (Arm A), where the lowest rate detection cutoff was 170 bpm and the delay to therapy initiation was programmed to 2.5 seconds. Importantly, neither treatment arm was associated with significantly increased syncope or mortality. The results of MADIT RIT firmly established preferred device settings for transvenous ICD (TV-ICD) patients with a primary prevention indication.

Preferred settings for subcutaneous ICDs, however, have not been established with data from prospective studies. The UNTOUCHED study will test a programming scheme designed to minimize inappropriate and unnecessary shocks in patients who have an indication for primary prevention of sudden cardiac death and low ejection fraction. Although S-ICD programming options do not permit exact replication of the programmed settings previously shown to reduce shocks in MADIT RIT Arms B and C, key elements of each programming scheme tested in MADIT RIT are combined into the UNTOUCHED settings to be tested in this protocol (see Table 3-1).

Table 3-1. Summary of UNTOUCHED and MADIT RIT Programmed Settings.

Detection Rate (BPM)	UNTOUCHED	MADIT RIT		
		A **Std. Programming**	**B** **High Rate Cutoff**	**C** **Long Delay**
170-199	**No Therapy**	Delay: 2.5s SVT Discriminators: ON Therapy: ATP[2]+Shock	**No Therapy**	Delay: 60s SVT Discriminators: ON Therapy: ATP+Shock
200-249	Delay: ≈**19.5s**[3] SVT Discriminators: **ON** Therapy: **Shock**	Delay: 1s SVT Discriminators: OFF Therapy: ATP+Shock	Delay: 2.5s SVT Discriminators: OFF Therapy: ATP+Shock	Delay: 1**2.5s** SVT Discriminators: **ON** Therapy: ATP+Shock
≥250	Delay: ≈**19.5s** SVT Discriminators: **OFF** Therapy: **Shock**			Delay: 2.5s SVT Discriminators: **OFF** Therapy: ATP+Shock

[2] In this table "Quick Convert" ATP is not distinguished from other forms of programmable ATP.
[3] For the S-ICD, delay is not a programmable value. The 19.5 second delay is an estimate derived from the mean time to therapy in spontaneous episodes recorded in the S-ICD Clinical Investigation (DN-17349 S-ICD® System Clinical Investigation Clinical Study Report, Revision E; November 6, 2013. Data on file at Boston Scientific.)

It is hypothesized that despite the lack of anti-tachycardia pacing, the EMBLEM™ S-ICD settings described in Table 3-1 will result in inappropriate and overall shock incidence similar to that observed in ICD patients from MADIT RIT arms B and C.

4 Device Description

The following information is a brief summary of the EMBLEM™ S-ICD System and its principle of operation. Refer to the applicable User's Manuals for additional information.

The EMBLEM™ S-ICD System is an implantable defibrillator system that treats ventricular tachyarrhythmias using a subcutaneous pulse generator and a subcutaneous electrode. The full EMBLEM™ S-ICD System consists of four devices that comprise the study device system:

- EMBLEM™ S-ICD Pulse Generator (Model A209) or later generation approved BSC S-ICD pulse generator[4]
- EMBLEM™ S-ICD Subcutaneous Electrode (Model 3401), Q-TRAK Electrode (Model 3010) or later generation approved BSC S-ICD electrode[4]
- EMBLEM™ S-ICD Electrode Insertion Tool, (Model 4711), Q-GUIDE Electrode Insertion Tool Model (Model 4010), or later generation approved BSC electrode insertion tool[4]
- EMBLEM™ S-ICD Programmer, (Model 3200) or other approved programmer capable of interrogating BSC S-ICD Systems[4]

The EMBLEM™ S-ICD System is designed to work with the following accessories:

- Programmer telemetry wand;
- Magnet;
- Suture sleeve, included in the electrode package;
- Torque wrench, included in the pulse generator package;
- SD memory card.

The EMBLEM™ S-ICD System also involves the use of a surface ECG based screening tool, which is used to determine the adequacy of sensing in potential candidates for an S-ICD.

Alternatively the integrated screening tool can be used, once available.

[4] Over the course of this study, new model numbers of each device may be introduced. The intention of this protocol is to allow the use of newer, functionally equivalent models that are market approved by the regulatory authorities in the country of the study center.

4.1 *EMBLEM™ S-ICD Pulse Generator*

The EMBLEM™ S-ICD pulse generator comprises an inner structure of discrete electrical components, interconnected hybrid assemblies, batteries, and high energy capacitors. The inner assembly is enclosed in a hermetically sealed can with a pre-moulded polyurethane header for electrode connection. The header contains a single port for connection of the subcutaneous electrode to accommodate sensing, pacing, and defibrillation. The EMBLEM™ S-ICD pulse generator is designed to provide high energy defibrillation shocks using a constant tilt biphasic waveform and is capable of delivering bradycardia demand pacing for a period up to thirty seconds following defibrillation therapy. Future generations of the BSC S-ICD pulse generator approved by the appropriate regulatory bodies may be included in the study.

4.2 *EMBLEM™ S-ICD Subcutaneous Electrode*

The EMBLEM™ S-ICD subcutaneous electrode features one high voltage defibrillation coil for the purpose of providing defibrillation energy. It is constructed using multifilars of metallic wire formed into a coil. Two sense electrodes (proximal and distal) are used for sensing. These sense electrodes are electrically insulated from the shock electrode by a multi-lumen polymeric tube.

Electrical connectivity to the pulse generator is provided using multiple strands of insulated metallic cable inserted into the same multi-lumen polymeric tube. This tube comprises the body of the subcutaneous electrode and is subcutaneously implanted from the device pocket along the rib margin to the sternum. The proximal termination comprises a multi-pole connector to plug into the header of the BSC S-ICD pulse generator. The connector is designed to be compatible with the BSC S-ICD pulse generators only. Future generations of the BSC subcutaneous electrode approved by the appropriate regulatory bodies may be included in the study.

4.3 *EMBLEM™ S-ICD Electrode Insertion Tool (EIT)*

The EMBLEM™ S-ICD EIT is a single use, disposable subcutaneous tunneling tool that is used to facilitate predictable placement of the subcutaneous electrode. The EIT is designed to create an appropriately sized subcutaneous sinus for the subcutaneous electrode such that the electrode will fit securely and not loosely in the subcutaneous sinus. The tip of the EIT and the tip of the subcutaneous electrode are equipped with suture holes which enable the two devices to be temporarily sutured together during the implant procedure. Once the two devices are sutured together, the EIT can be used to pull the subcutaneous electrode through a subcutaneous sinus. Future generations of the BSC subcutaneous electrode insertion tool approved by the appropriate regulatory bodies may be included in the study.

4.4 *EMBLEM™ S-ICD Programmer*

The programmer is a completely self-contained, non-sterile, non-implantable, lightweight, easily portable computer that does not allow general purpose computing. It implements a graphical user interface (GUI) design which gathers user input via touch screen. Communication between the pulse generator and the programmer is accomplished through an RF telemetry wand. The radio link operates in the Medical Implant Communication Service band specified in EN 301 839-1:2002 and complies with applicable FCC regulations. The programmer is capable of recognizing multiple pulse generators, but active communication is permitted with only one pulse generator at a time. Communication between the programmer and a printer is based on a standard Bluetooth piconet.

The programmer application consists of multiple screens from which online (active communication with the pulse generator) and offline modes may be commanded. Programmer functionality includes:

- Scan for devices, resulting in a display of pick list of pulse generators
- Establishment and termination of communication link
- Display of a real-time S-ECG
- Selection of programmable parameters
- Review of subject event history

Future generations of the BSC programmer approved by the appropriate regulatory bodies may be included in the study.

5 Objectives

The primary objective is to assess the 18 month incidence of inappropriate shocks in subjects implanted with the EMBLEM Subcutaneous Implantable Defibrillator (S-ICD) programmed with zone cutoffs at 200 bpm and 250 bpm, and:

- an indication for implantation of a defibrillator for primary prevention of sudden cardiac death;
- a left ventricular ejection fraction $\leq 35\%$.

The 18 month incidence rate will be compared to an *Objective Performance Criteria* derived from transvenous ICDs programmed to minimize shocks in the MADIT RIT study.

The secondary objectives are to assess the 18 month incidence of all-cause shocks and to assess perioperative complications.

Device and procedure related complications at 6 months and implant success rate at 3 months will also be assessed to fulfill *Post Market Clinical Follow-up* (PMCF) requirements.

6 Study Endpoints and Analyses

6.1 *Primary Endpoint*

The primary endpoint is the Inappropriate Shock Free Rate at 18 months compared to a performance goal of 91.6%.

6.2 *Secondary Endpoint*

The secondary endpoints are:

- All-Cause Shock Free Rate at 18 months compared to the performance goal of 85.8%.
- Freedom from System and Procedure Related Complications at 30 days compared to a performance goal of 93.8%.

6.3 *Post Market Clinical Follow-up (PMCF) Endpoint*

The PMCF endpoint is Freedom from System and Procedure Related Complications at 6 months compared to a performance goal of 85%. Additionally, the implant success rate through 3 months will be reported.

6.4 *Additional Pre-Specified Analyses*

Additional pre-specified analyses include:

- Freedom from Appropriate Shocks at 18 months
- All-cause mortality
- Syncope related to VT/VF episodes
- Implantation of a concomitant pacemaker
- Explants and causes

7 Design

The UNTOUCHED Study is a global, multi-site, prospective, non-randomized study that will enroll subjects who intend to undergo de novo implantation of an EMBLEM™ S-ICD System and have an indication for primary prevention of sudden cardiac death with a left ventricular ejection fraction ≤ 35%. Subjects will be implanted with an EMBLEM or later generation BSC S-ICD that is programmed with zone cut-offs at 200 bpm (Conditional Shock Zone) and 250 bpm (Shock Zone) and followed semi-annually for a minimum of 540 days (i.e., 18 months) post implant. Subject participation will end after a follow-up visit has been recorded at least 540 days after the index implant procedure.

7.1 *Scale and Duration*

The study will be conducted at up to 200 sites worldwide. At least 1.100 subjects will be enrolled. Sites may continue to enroll subjects until notified of enrollment completion. The duration of the study, from first enrollment to last patient follow-up visit is expected to be 51 months. The duration from first enrollment to study closure is expected to be approximately 58 months.

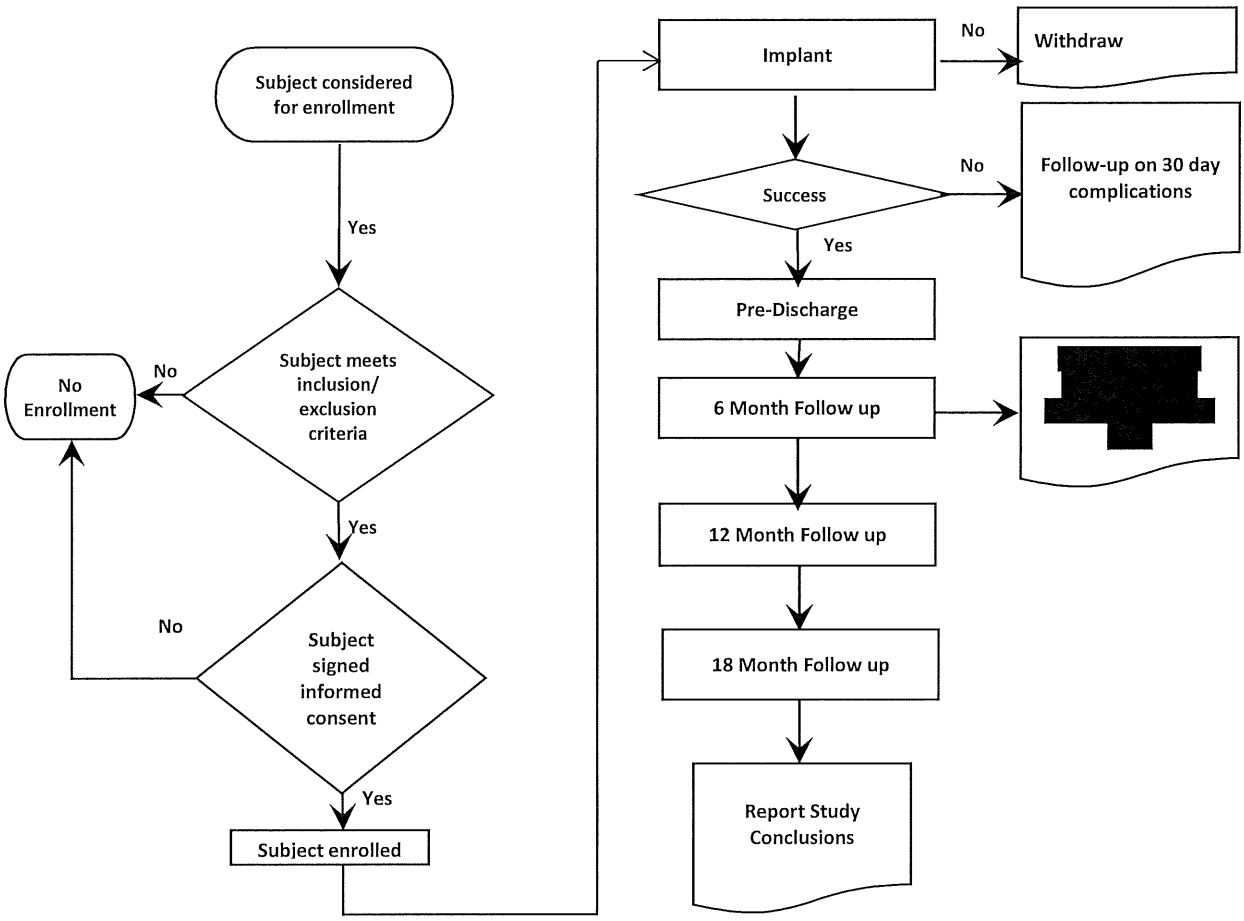


Figure 7.1-1: UNTOUCHED Study Design

7.2 *Treatment Assignment*

Devices used in the UNTOUCHED study are all commercially available. Investigators are responsible for screening eligible patients with an indication for an S-ICD system. Any patient meeting the inclusion criteria and not meeting the exclusion criteria below should be considered for enrollment in the UNTOUCHED study. Patients are considered enrolled in the study once the consent form has been signed.

7.3 *Justification for the Study Design*

The UNTOUCHED Study is designed to assess the incidence of shocks and complications in patients who have an indication for primary prevention of sudden cardiac death and a low ejection fraction who are implanted with an EMBLEM™ S-ICD. Studies with transvenous ICDs conducted in a similar patient population (e.g. MADIT RIT) have shown that programmed device settings can significantly reduce the overall number of patients who receive a transvenous ICD shock. This study is intended to similarly test programmable S-ICD settings in a non-randomized study design to compare shock and complication outcomes with objective performance criteria derived from transvenous ICD studies.

8 Subject Selection

8.1 *Study Population and Eligibility*

The study population consists of patients:

- with an ICD indication for primary prevention of sudden cardiac death and a reduced ejection fraction; and
- who are at risk for life-threatening ventricular tachyarrhythmias and who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.

8.2 *Inclusion Criteria*

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

Table 8-1: Inclusion Criteria

Clinical Inclusion Criteria	• Patient with ischemic or non-ischemic heart disease who meets current guidelines for ICD therapy and intends to undergo a de novo implant procedure for an EMBLEM™ S-ICD (or newer generation BSC S-ICD) • Left ventricular ejection fraction ≤ 35% • A passing EMBLEM™ S-ICD (or newer generation BSC S-ICD) screening ECG • Patient ≥ 21 years of age willing and capable of giving informed consent • Patient willing and capable of complying with follow-up visits

8.3 *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8-2) will be excluded from this clinical study.

Table 8-2: Exclusion Criteria

Clinical Exclusion Criteria	• Patient with a history of spontaneous sustained VT or VF • Patient with bradycardia pacing indication • Patient eligible and scheduled for cardiac resynchronization implant • Patient with a previous S-ICD or a previous transvenous pulse generator (pacemaker or defibrillator) • Patient in NYHA Class IV documented in the medical records within 90 days before enrollment • Patient with life expectancy shorter than 18 months due to any medical condition (e.g., cancer, uremia, liver failure, etc…) • Patient receiving hemodialysis within 180 days before to enrollment • Patients unable to give consent in person, including patients unable to read or write • Patient who is known to be pregnant or plans to become pregnant over the course of the trial • Patient unwilling or unable to cooperate with the protocol • Participation in concurrent clinical study without prior approval from Boston Scientific • Medical status (e.g., hemodynamic conditions) of the patient doesn't allow programming devices with a conditional shock zone at 200 bpm and a shock zone at 250 bpm, in the judgment of the implanting physician and/or according to (inter)national guidelines.

9 Subject Accountability

9.1 *Point of Enrollment*

Subjects will be considered enrolled after providing written informed consent. Patients consented but who finally will not undergo an implant procedure, regardless whether successful or not, will not be counted towards the minimum required sample size.

9.2 *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 on the End of Study case report form. eCRFs up to the point of withdrawal will be collected. No additional data may be collected after the withdrawal time point.

9.3 *Loss to Follow-Up*

For patients considered lost to follow-up, documentation of attempts to contact the patients must be retained. Three attempts to contact the patient must be documented.

9.4 *Subject Status and Classification*

Any patient having signed a patient consent form is considered enrolled. Intent patients will not count towards the enrollment ceiling. Subject status will be classified as below after enrollment:

- **Intent:** A subject who has been enrolled, but does not have anaesthesia administered in preparation for a BSC S-ICD System implant procedure. The original Informed Consent form and screening documentation for intent patients should be maintained in the Center's files and an *End of Study* form completed. Also includes a subject who has signed the informed consent but is found to not meet eligibility criteria and either undergoes or does not undergo an implant and/or any study related procedure. Patients shall be withdrawn from the study and followed as per standard of care. No further follow-up is required.

- **Partial Attempt**: A subject who has been enrolled and has had anaesthesia administered in preparation for a BSC S-ICD System implant procedure, but does not undergo an implant/main study procedure. The patient shall be contacted at least 30 days after the attempt to check for any reportable adverse event possibly related to the partial attempt and an *End of Study* form completed. No further follow-up is required after the 30 day contact.

- **Attempt:** A subject who has been enrolled, had anaesthesia administered in preparation for a BSC S-ICD System implant procedure, undergoes a BSC S-ICD System implant

procedure, but is not successfully implanted with the study device. Reportable adverse events shall be collected for the subject until 30 days from the attempted implant procedure. The subject will be included in data analysis for the implant success rate. An *End of Study* form shall be completed. No further follow-up is required after the 30 day contact.

- **Implant:** A subject who has been enrolled and is successfully implanted with a BSC S-ICD System.

9.5 *Enrollment Controls*

Investigational sites will be notified to cease enrolling subjects when at least 1,100 subjects have been entered in the database and an implant procedure was performed regardless whether successful or not. Patients consented but who finally will not undergo an implant procedure will not count towards the 1100 patients. Patients already consented at time of notification shall still be entered in the database and followed per study protocol. No single site is to enroll more than 10% (110 patients) without the prior written approval of Boston Scientific.

10 Study Methods

10.1 *Data Collection*

Data will be collected from each subject at enrollment, implant, pre-discharge, and semi-annual follow-up visits through at least 540 days (18 months) post implant. Additional follow-up visits must be collected if they are associated with a reportable adverse - event, treated device episode, suspected device deficiency, or device programming change. Routinely scheduled office visits, for purposes other than the aforementioned events, do not require additional visit forms to be completed.

Spontaneous episodes can be collected via the Latitude® NXT System, if applicable, but this does not replace the semi-annual in clinic visits, nor does it replace the requirement to upload all device episodes in the study database. The data collection schedule is shown in Table 10-1.

Table 10-1: Data Collection Schedule

	Enrollment Visit (No window)	Implant (No window)	Pre-Discharge (No window)	Semi-Annual Follow-up (Day 180-240; Day 360-420; Day 540-600 from implant)	Additional Follow-up (No Window)	Additional Implant (No Window)	End of Study (No Window)
Consent Date	X						
Baseline Characteristics	X						
Cardiovascular Medications	X						
Screening ECG	X						
Implant Details		X				X	
Follow-Up Details			X	X	X	X	X
S-ICD System Parameters		X	X	X	X	X	X
Reportable AEs / Device Deficiencies	*	*	*	*	*	*	*
Protocol Deviations	*	*	*	*	*	*	*
Spontaneous Episodes		*	*	*	*	*	*

X = required; * =data entered only if the event occurred.

10.2 *Study Candidate Screening*

Investigators are responsible for screening patients eligible for an EMBLEM™ S-ICD implant procedure. The implant procedure must be a de novo implantation of an EMBLEM™ S-ICD System. Any patient meeting the inclusion criteria and not meeting the exclusion criteria should be considered for enrollment in the UNTOUCHED study. A formal screening log is not required to be maintained.

Preoperative S-ICD Screening ECGs (in all leads and postures evaluated) shall be retained for all enrolled subjects EMBLEM™ S-ICD.

10.3 *Informed Consent and Enrollment*

Patients are considered enrolled in the study once the consent form has been signed. No data collection, data entry, or study specific procedure shall be performed prior to having appropriately consented the patient.

Preoperative S-ICD Screening ECGs (in all leads and postures evaluated), subject demographics, medical history and cardiovascular medications will be collected for all enrolled subjects. Table 10-2 lists the data collected at the enrollment visit.

Table 10-2: Enrollment Data Collection

Data Collection	Retention of Original Source Documentation
Informed consent	Study center
Pre-operative S-ICD Screening ECG	Study center
Inclusion/Exclusion Criteria, Demographics, Medical History, Cardiovascular Medications	Study center

10.4 *Implant Procedure and Data Collection*

All enrolled subjects must undergo a de novo implant procedure for an EMBLEM™ S-ICD or future generation BSC S-ICD. Any subject receiving anesthesia in anticipation of the index implant procedure requires completion of an implant case report form. Implantation of the EMBLEM™ S-ICD System should be performed using the standard of care methods established by the study center. The EMBLEM™ S-ICD System User's Manual provides detailed instructions regarding the implantation and use of the EMBLEM™ S-ICD System.

Procedural data, peri-operative medication management, product information, VT/VF conversion test results (if applicable) and programmed parameters are to be collected at implant. Reportable adverse events, device deficiencies, and protocol deviations will be assessed and reported appropriately. Patients who are not implanted with an S-ICD System (i.e., classified as "Partial Attempt" or "Attempt"), are to be withdrawn from the study after a minimum of 30 days of follow up (see Section 10.9), which is documented on the *End of Study* form. Pulse Generators and electrodes used in the implant procedure but not implanted must be reported on an *Out of Service Device* form (see Section 10.8). Table 10-3 lists the data collected at the implant visit.

Table 10-3: Implant Data Collection

Data Collection	**Retention of Original Source Documentation**
Peri-operative medications (e.g., type of anesthesia) Implanted EMBLEM™ S-ICD System components (model/serial, etc.) Procedure and Operative notes If conversion testing was performed at the visit: - Induced VT/VF episode Induction S-ECG Report for all episodes shocked Reportable Adverse Events, Device Deficiencies, and Protocol Deviations if applicable	Study center
EMBLEM™ S-ICD Programmer Printouts: - Final Summary Report - Device Episode Report(s), if applicable	Study center; upload electronic copy to BSC

10.4.1 Conversion Testing

Conversion testing is not a requirement of this protocol; however, when conversion testing is performed, the Induction S-ECG Reports shall be printed and retained for each conversion attempt that results in a shock by the EMBLEM™ S-ICD. The retained Induction S-ECG Reports document whether a ≥15 joule safety margin was obtained (i.e., successful conversion with an EMBLEM™ S-ICD shock at 65 joules or less).

Any conversion testing that occurs throughout the duration of the study shall be recorded on a conversion testing form related to the concerned visit.

10.4.2 Required Programming and Device Setup

All implanted devices must be programmed with a Conditional Shock Zone set to 200 bpm, a Shock Zone set to 250 bpm and therapy "ON" prior to hospital discharge. These settings are to be maintained through the duration of the study. All other programming parameters (e.g., sensing vector, gain) are left to the discretion of the investigator.

10.5 *Pre-Discharge Data*

Pre-discharge refers to the timeframe from implant to time of discharge. The Final Summary Report, device episodes (if applicable), VT/VF conversion test results (if applicable), and follow up details are required at the pre-discharge visit. New medical devices or procedures that could potentially affect the performance of the S-ICD are also collected at the pre-discharge visit. **The final summary report collected at the pre-discharge visit must show the Conditional Shock Zone set to 200 bpm and the Shock Zone set to 250 bpm**. Reportable adverse events, device deficiencies, and protocol deviations will be assessed and reported appropriately. Additionally Table 10-4 summarizes the data required at the pre-discharge visit.

Table 10-4: Pre-Discharge Data Collection

Data Collection	Retention of Original Source Documentation
Reportable Adverse Events, Device Deficiencies and Protocol Deviations if applicable If conversion testing was performed at the visit: - Induced VT/VF episode Induction S-ECG Report for all episodes shocked	Study center
EMBLEM™ S-ICD Programmer Printouts: - Final Summary Report[5] - Device Episode Report(s), if applicable	Study center; upload copy to BSC

10.6 *Semi-Annual Follow-up Visit*

After implant, scheduled follow-up visits are to be performed semi-annually at 180 day intervals from the index implant procedure date (i.e., 180-240 days, 360-420 days and 540-600 days post implant) in order to capture new (not been previously reported):

- Spontaneous episodes;
- Reportable Adverse events;
- Programming changes;
- Device deficiencies;
- Protocol deviations.

The final summary report must show the Conditional Shock Zone set to 200 bpm, the Shock Zone set to 250 bpm and therapy "ON". New medical devices or procedures that could potentially affect the performance of the S-ICD are also collected at semi-annual visits, as are any VT/VF conversion test results (if applicable)..

Note that the scheduling windows for semi-annual follow-up visits begin at days 180, 360 and 540. This will ensure that subjects who complete the study per protocol contribute completely to survival analyses, rather than being censored prior to completion of key follow up intervals. Table 10-5 lists all the data required at semi-annual follow-up visits.

[5] The Final Summary Report at the pre-discharge visit must demonstrate that the patient was discharged with the device programmed according to Section 10.4.2 (Conditional Shock Zone set to 200 bpm and a Shock Zone set to 250 bpm).

Table 10-5: Semi-Annual Follow-Up Visit Data Collection

Data Collection	Retention of Original Source Documentation
Reportable Adverse Events, Device Deficiencies, and Protocol Deviations if applicable If conversion testing was performed at the visit: - Induced VT/VF episode Induction S-ECG Report for all episodes shocked	Study center
EMBLEM™ S-ICD Programmer Printouts: - Final Summary Report - Device Episode Report(s), if applicable	Study center; upload copy to BSC

10.7 *Additional Follow-up Visits*

Physician office visits, emergency room visits, out-patient hospital visits, and hospitalizations shall be recorded as an additional follow-up visit only if they are associated with a treated episode, system revision, device deficiency, reportable adverse event, protocol deviation or device programming change[6]. Other scheduled and unscheduled visits throughout the year (e.g., standard of care device checks) that do not meet these criteria are not required by the protocol. **Table 10-6** lists all the data required from additional follow-up visits.

The final summary report must show the Conditional Shock Zone set to 200 bpm, the Shock Zone set to 250 bpm and therapy "ON". New medical devices or procedures that could potentially affect the performance of the S-ICD are also collected at additional follow-up visits, as are any VT/VF conversion test results (if applicable).

An additional follow-up visit captures new (not been previously reported):

- Treated spontaneous episodes;
- Reportable Adverse events;
- Programming changes;
- Device deficiencies;
- Protocol deviations.

Table 10-6. Additional Follow-Up Visit Data Collection

[6] A programming change refers to any difference between *Initial Device Settings* and *Current Device Settings* under the *Programmable Parameters* section of the device Summary Report.

Data Collection	Retention of Original Source Documentation
Reportable Adverse Events, Device Deficiencies, and Protocol Deviations if applicable If conversion testing was performed at the visit: - Induced VT/VF episode Induction S-ECG Report for all episodes shocked	Study center
EMBLEM™ S-ICD Programmer Printouts: - Final Summary Report - Device Episode Report(s), if applicable	Study center; upload copy to BSC

10.8 *Out of Service (OOS) Devices*

If either the PG or electrode is removed from service (e.g., device not successfully implanted or device explanted) or the subject expires, an OOS device form is required. Subjects whose device is explanted with no intention of replacement with another BSC S-ICD (or component) should be withdrawn from the study according to the requirements of Section 10.9. For deceased subjects, every effort should be made to collect a final summary report and any episodes recorded by any PG taken out of service. Table 10-7 lists all the data required for out of service device data collection.

Table 10-7. Out of Service Device Data Collection

Data Collection	Retention of Original Source Documentation
Out of Service Device Information	Study center
Reportable Adverse Events, Device Deficiencies, and Protocol Deviations if applicable	Study center
EMBLEM™ S-ICD Programmer Printouts (if available): - Final Summary Report - Device Episode Report(s), if applicable	Study center; upload copy to BSC

10.9 *Study Completion*

Subject participation in the study is considered complete for the following reasons:

- **Study completion per protocol** (e.g., a follow-up visit has been recorded at least 540 days from the date of the index implant procedure);
- **Death** (see Section 19.5 for reporting requirements);
- **Withdrawal** for reasons that include, but are not limited to:
    - Subject found not to meet eligibility criteria;
    - Unable to implant study device (i.e., the subject is not implanted with the EMBLEM™ S-ICD System and is classified as a partial attempt or attempt);
        - Prior to completing the study, the subject will be contacted, either in person or by telephone, at least 30 days after the failed implant attempt in order to capture any reportable adverse events.
    - Subject withdrawal of consent.
    - Explant of the EMBLEM™ S-ICD PG and/or Electrode and not replaced with another BSC S-ICD PG and/or Electrode;
        - Prior to completing the study, the subject should be contacted, either in person or by telephone, at least 30 days after the permanent explant in order to capture any reportable adverse events.
    - Heart transplant.
    - Investigator discretion.
    - Lost to follow-up, despite best efforts to locate the subject;
        - Three documented attempts to contact the subject are required to declare a subject lost to follow up.

Table 10-8 lists all the data that are required for study completion.

Table 10-8. Study Completion Data Collection

Data Collection	Retention of Original Source Documentation
Reportable Adverse Events, Device Deficiencies, and Protocol Deviations if applicable	Study center
EMBLEM™ S-ICD Programmer Printouts: - Final Summary Report - Device Episode Report(s), if applicable	Study center; upload copy to BSC

10.10 *Source Documents*

Original source documents should be maintained. If original source documents including, but not limited to, printouts of original electronic source documents are retained, copies shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document. This requirement is not applicable to printouts from the programmer, external defibrillator or ECG machine.

11 Statistical Considerations

11.1 *Endpoints*

The sample sizes for the primary endpoint and the secondary effectiveness and safety endpoints are based on the sample size not including subjects with permanent atrial fibrillation. Section 11.3.2 explains how the subgroup of subjects with permanent atrial fibrillation will be handled for analysis purposes.

11.1.1 Primary Endpoint

The primary endpoint is the Inappropriate Shock Free Rate at 540 days (18 months) compared to a performance goal of 91.6%.

11.1.1.1 Hypotheses

The primary endpoint null and alternative hypotheses are as follows:

Ho: The Shock Free Rate at 540 days (p1) does not exceed the performance goal of 91.6%.

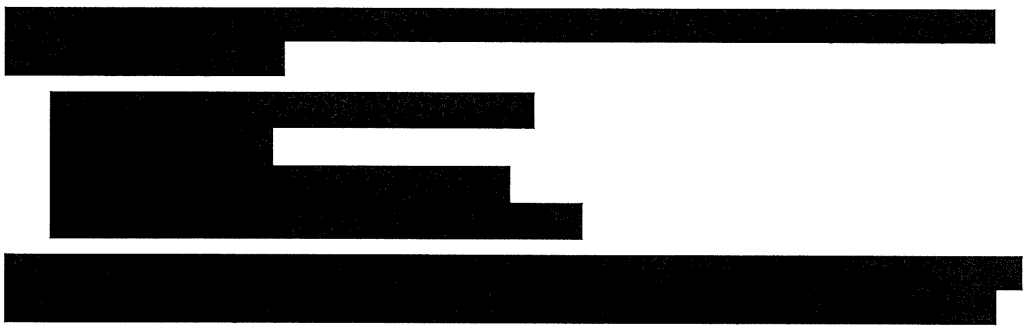
$$Ho: p1 \leq 91.6\%$$

Ha: The Shock Free Rate at 540 days (p1) does exceed the performance goal of 91.6%.

$$Ha: p1 > 91.6\%$$

The null hypothesis will be rejected if the lower one-sided 95% confidence bound[7] of the Kaplan-Meier estimate exceeds the performance goal of 91.6%.

11.1.1.2 Sample Size



[7] Using the Peto estimate for the standard error.

11.1.1.3 Statistical Methods

The primary endpoint will be evaluated as proportions of subjects free from events based on the Kaplan-Meier method including the one-sided lower 95% confidence interval[8]. Only episodes adjudicated to be inappropriately treated and recorded by the device counters will be used toward the endpoint.

Two Kaplan-Meier analyses will be done:

- One will take into account the time from implant until the occurrence of the event and data from any subjects who are event-free will be right censored on the date of study exit.
- The other will also take into account the time from implant until the occurrence of the event, but will right censor subjects whose device programming deviates from the protocol required programming (e.g., Conditional Shock Zone not 200 bpm, Shock Zone not 250 bpm, or device turned off for more than 24 consecutive hours) at the time of reprogramming or when the initial implanted device is taken out of service.

11.2 *Secondary Effectiveness Endpoint*

The secondary effectiveness endpoint is the All-Cause Shock Free Rate at 540 days (18 months) compared to a performance goal of 85.8%.

11.2.1.1 Hypotheses

The secondary effectiveness endpoint null and alternative hypotheses are as follows:

Ho: The Shock Free Rate at 540 days (p1) does not exceed the performance goal of 85.8%.

$$\text{Ho: } p1 \leq 85.8\%$$

Ha: The Shock Free Rate at 540 days (p1) does exceed the performance goal of 85.8%.

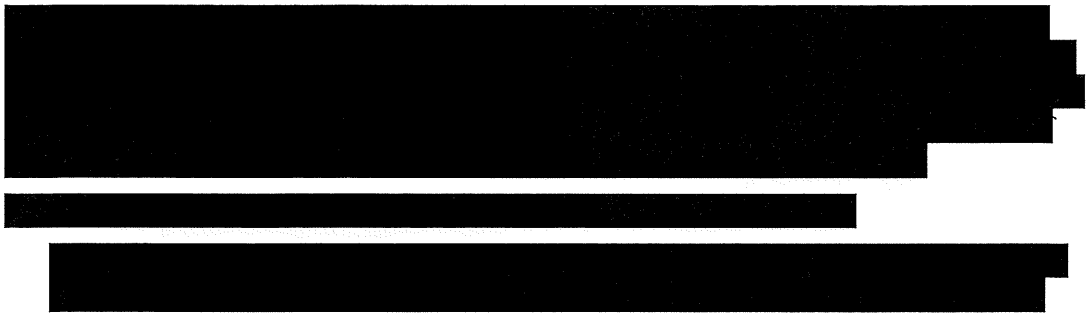
$$\text{Ha: } p1 > 85.8\%$$

The null hypothesis will be rejected if the lower one-sided 95% confidence bound[8] of the Kaplan-Meier estimate exceeds the performance goal of 85.8%.

11.2.1.2 Sample Size

[redacted]

[8] Using the Peto estimate for the standard error.



11.2.1.3 Statistical Methods

The same methodology outlined in section 11.1.1.3 will be used for this endpoint. Only spontaneous episodes treated and recorded by the device counters will be used toward the endpoint. Induced episodes shocked by the subcutaneous system or episodes treated with an external defibrillator will not count.

11.3 *Secondary Safety Endpoint*

The secondary safety endpoint is Freedom from System and Procedure Related (Type I) Complications at 30 days compared to a performance goal of 93.8%.

11.3.1.1 Hypotheses

The secondary safety endpoint null and alternative hypotheses are as follows:

Ho: The System and Procedure Related (Type I) Complication Free Rate at 30 days (p1) does not exceed the performance goal of 93.8%.

$$Ho: p1 \leq 93.8\%$$

Ha: The System and Procedure Related (Type I) Complication Free Rate at 30 days (p1) does exceed the performance goal of 93.8%.

$$Ha: p1 > 93.8\%$$

The null hypothesis will be rejected if the lower one-sided 95% confidence bound of the Kaplan-Meier estimate exceeds the performance goal of 93.8%.

11.3.1.2 Sample Size

11.3.1.3 Statistical Methods

The secondary safety endpoint will be evaluated as proportions of subjects free from events based on the Kaplan-Meier method including the one-sided lower 95% confidence interval.

The Kaplan-Meier analysis will take into account the time from implant until the occurrence of the event and data from any subjects who are event-free will be right censored on the date of study exit. Analysis of the secondary endpoint will be done in conjunction with the next annual report following the completion of 30 day follow up visits of at least 427 de novo S-ICD subjects. All de novo S-ICD subjects who have completed the 30 day follow up at the time of the data lock will be included in the analysis.

11.4 *Post Market Clinical Follow Up (PMCF) Endpoint*

The PMCF endpoint is Freedom from System and Procedure Related Complications (Type I) at 180 days (6 months) compared to a performance goal of 85%.

11.4.1.1 Hypotheses

The PMCF endpoint null and alternative hypotheses are as follows:

Ho: The System and Procedure Related (Type I) Complication Free Rate at 180 days (p1) does not exceed the performance goal of 85.0%.

$$Ho: p1 \leq 85.0\%$$

Ha: The System and Procedure Related (Type I) Complication Free Rate at 180 days (p1) does exceed the performance goal of 85.0%.

$$Ha: p1 > 85.0\%$$

The null hypothesis will be rejected if the lower one-sided 95% confidence bound[9] of the Kaplan-Meier estimate exceeds the performance goal of 85.0%.

[9] Using the Peto estimate for the standard error.

11.4.1.2 Sample Size

[redacted]

11.4.1.3 Statistical Methods

The PMCF endpoint will be evaluated as proportion of subjects free from events based on the Kaplan-Meier method including the one-sided lower 95% confidence interval.

The Kaplan-Meier analysis will take into account the time from implant until the occurrence of the event and data from any subjects who are event-free will be right censored on the date of study exit. Analysis of the PMCF endpoint will be done when 200 de novo S-ICD subjects have a follow up visit recorded at least 180 days after implant.

11.5 *Additional PMCF Endpoint*

The 90-day (3 month) implant success rate will be documented as percentage of de novo S-ICD subjects with an implanted device at 90 days out of the total number of subjects included in the PMCF endpoint analysis. No minimum sample size is required for evaluation of the implant success rate. Summary statistics will be calculated.

11.6 *Sample Size Summary*

[redacted] Therefore the total study sample size will be a minimum of 1100 subjects.

11.7 *General Statistical Methods*

11.7.1 Analysis Sets

The primary and secondary effectiveness endpoint analyses will include all subjects who are implanted. Additional analyses will be performed to assess the impact of protocol deviations for programming contrary to the required programmed settings, as specified in Section 11.2.1.3.

The secondary endpoint analysis will include all de novo S-ICD subjects (i.e., subjects undergoing their first ICD implantation and not a replacement of a prior TV-ICD or S-ICD) who are implanted or have an attempted implant at the time of the data analysis.

The PMCF endpoint analyses will include the first 200 de novo S-ICD subjects (i.e., subjects undergoing their first ICD implantation and not a replacement of a prior TV-ICD or S-ICD) who are implanted or have an attempted implant.

11.7.2 Control of Systematic Error/Bias

Selection of subjects for enrollment will be made from the Investigator's usual patient population. All subjects meeting the eligibility criteria and having signed the ICF will be enrolled in the study. To control for the potential bias, an independent medical reviewer will adjudicate key endpoint related events submitted by study centers.

11.7.3 Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 10% (n=110) of the total enrollment target without approval from Boston Scientific.

11.8 *Data Analyses*

11.8.1 Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. Analysis of each endpoint will be performed when sufficient data have been collected to meet the power requirements of each endpoint or the study has completed.

11.8.2 Pooling Analyses

It is expected that results may differ for subjects with permanent atrial fibrillation compared to those without atrial fibrillation or with non-permanent atrial fibrillation. In order to confirm the poolability these groups, a pooling analysis will be performed. Specifically, a likelihood ratio test from a logistic regression model will be conducted.

The logistic regression model will include additional baseline covariates to attempt to adjust for any imbalances between baseline data. The following baseline covariates will be considered: age, gender, race, LVEF, NYHA classification, medications, arrhythmia history, associated diseases/risk factors, height, weight and geography. To determine which covariates are significantly associated with an endpoint, a backwards selection process will employed, using a significance level equal to 10%.

If poolability is confirmed for permanent atrial fibrillation subjects, then the study results will be reported combining all subjects.

11.8.3 Other Endpoints/Measurements

Summary statistics will be provided for the following:

- Freedom from Appropriate Shocks at 18 months
- All-cause mortality
- Syncope related to VT/VF episodes
- Implantation of a concomitant pacemaker
- Explants and causes (e.g., infection, need for pacing therapy, inappropriate shocks)

11.8.4 Changes to Planned Analyses

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

12 Data Management

12.1 *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. All case report forms for study visits should be submitted within 10 business days of the visit, unless reportable events require shorter reporting timelines (see Section 19.3).

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) 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.

12.2 *Data Retention*

The Investigator or his/her designee or the 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 for at least 2 years after the study has been formally closed. These documents will be retained in compliance with other local regulations. The Investigator will take measures to ensure that these essential documents are not

accidentally damaged or destroyed. If for any reason the Investigator 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.

13 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) of the revised protocol must be obtained prior to implementation.

14 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor 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. 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, center re-training, or discontinuation) will be put into place by the sponsor.

Deviations will be classified according to the following definitions:

- Type A - Deviation to protect the life or physical well-being of a patient in an unforeseen emergency.
- Type B - Deviation based on medical judgment.
- Type C - Deviation due to misunderstanding of protocol requirements.
- Type D - Deviation due to a situation that is beyond control.
- Type E - Deviation due to an oversight, error or protocol non-compliance.

15 Device/Equipment Accountability

Devices used within the UNTOUCHED study are commercially available. Device use within the study will be tracked by model and serial number together with the patient identifier. Device stickers (model/serial number) should be attached to the implant source documentation, if available.

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 14155:2011, 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/Site Selection Criteria*

The sponsor will consider many factors to ensure selection of sites and investigators that are qualified through their training and experience to properly conduct the study. Diverse sites will be selected with respect to geography and clinical setting. The current BSC process for evaluating and selecting clinical sites will be utilized. The evaluation and selection criteria include but are not limited to the following:

- Sites that have the personnel with knowledge to run a clinical study and enroll subjects according to good clinical practice guidelines. It is recommended that sites have a dedicated Research Coordinator and exceptions will be evaluated on a case-by-case basis
- Sites that have a Principal Investigator (physician) who has a commitment to conducting research
- Sites that have the necessary knowledge and experience to implant the EMBLEM™ S-ICD
- Sites that have the potential subject volume to meet enrollment expectations
- Site personnel that have a commitment to protocol compliance along with gathering and submitting timely and accurate data using an electronic data entry system
- Sites that will support on-site clinical data monitoring during the study

16.3 *Investigator Responsibilities*

The Principal Investigator of an study center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, applicable sections of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject. The Principal Investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the Clinical Study Agreement and 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 center 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 reportable adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to an SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to an SADE, 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.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- 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.

16.3.1 Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the 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. Delegated tasks must be appropriately documented in the Site Signature Responsibility Log. Members of the study team must not perform tasks delegated to them by the Investigator until completion of all pertinent trainings.

16.4 *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the study center 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. The sponsor will provide an "Approval to Enroll" letter once all documentation is complete.

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.

16.5 *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 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' 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.

16.5.1 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 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
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data fromprogrammers and other equipment

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 HCP
- 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

16.6 *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 on site or remotely during the study to assess continued compliance with the protocol and applicable regulations. During monitoring visits the 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively and has adequate oversight of trial conduct. The 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 expected that the 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*

Patients participating in the UNTOUCHED study have a number of concomitant diseases as part of their underlying condition, not limited to diabetes, cancer/tumors, multiple sclerosis, allergies, osteoporosis, arthritis, emphysema, vision or aural problems, rectal polyps, peripheral artery disease, chronic obstructive pulmonary disease, renal failure, they also might experience pain due to musculoskeletal injuries unrelated to arrhythmias or device function, muscle aches due to over-exertion, joint degeneration, tendonitis and bursitis, and burns from external causes. They also might experience age or infection related adverse events like gastrointestinal ulcers, hemorrhoids, immune system deficiencies like HIV or AIDS, infectious diseases like hepatitis or herpes viruses, neurological/psychological disorders such as Alzheimer's, Parkinson's, dementia, obsessive/compulsive disorder or eating disorders. Other illnesses would include jaundice unrelated to systemic infection, infection in extremities unrelated to procedure, bacterial infection or cellulitis. Other common conditions include headache, muscle pain, food poisoning, superficial infections, rashes, warts, shingles, constipation, eczema, hernias, upper respiratory infections, or influenza. Relationship to the study device or procedure are unlikely. The list below contains Anticipated Adverse Events potentially related to the study device or procedure.

The following anticipated adverse events (AE) have been identified for this study.

- Acceleration/induction of atrial or ventricular arrhythmia
- Adverse reaction to induction testing
- Allergic/adverse reaction to system or medication
- Bleeding
- Conductor fracture
- Cyst formation
- Death
- Delayed therapy delivery
- Discomfort or prolonged healing of incision
- Electrode deformation and/or breakage
- Electrode insulation failure
- Erosion/extrusion
- Failure to deliver therapy
- Fever
- Hematoma/seroma
- Hemothorax
- Improper electrode connection to the device
- Inability to communicate with the device
- Inability to defibrillate or pace
- Inappropriate post shock pacing
- Inappropriate shock delivery
- Infection
- Keloid formation
- Migration or dislodgement
- Muscle/nerve stimulation
- Nerve damage
- Pneumothorax
- Post-shock/post-pace discomfort
- Premature battery depletion
- Random component failures
- Stroke
- Subcutaneous emphysema
- Surgical revision or replacement of the system
- Syncope
- Tissue redness, irritation, numbness or necrosis
- If any adverse events occur, invasive corrective action and/or S-ICD System modification or removal may be required.
- Patients who receive an S-ICD System may develop psychological disorders that include, but are not limited to, the following:
    - Depression/anxiety
    - Fear of device malfunction
    - Fear of shocks
    - Phantom shocks

18.2 *Anticipated Adverse Device Effects*

Adverse Device Effects that are part of the listing in the previous paragraph 18.1 are to be considered Anticipated Adverse Device Effects.

18.3 *Risks associated with Participation in the Clinical Study*

The UNTOUCHED study includes the requirement to program devices with a conditional shock zone at 200 bpm and a shock zone at 250 bpm. These values are within the approved ranges of programmable settings and are in the range of the Tachycardia Detection Programming Recommendations[11] and also reported in the literature[10]. The risks related to S-ICD therapy are the ones expected for the study population and have been listed under 18.1 Anticipated Adverse Events. No specific risks in addition to those mentioned in the listing are to be expected with participation in the UNTOUCHED study.

18.4 *Risk Minimization Actions*

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

18.5 *Anticipated Benefits*

The programming of EMBLEM™ S-ICD Systems according to this protocol is hypothesized to reduce the number of unnecessary or inappropriate shocks.

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, and the intention is to decrease the incidence of inappropriate shocks in primary prevention patients implanted with an EMBLEM (or later generation) S-ICD. The proposed programming in the UNTOUCHED study (Conditional Shock Zone of 200 and Shock Zone of 250) were available programming options in the IDE Study and EFFORTLESS registry used for the pooled analysis on S-ICD studies. The median lowest rate zone in this pooled analysis was 200 bpm as chosen by Investigators, which was not required by the protocol[10]. Additionally both of these programmed zones were used in the MADIT RIT trial without increased risk.

Further, the recently published Expert Consensus Statement on Optimal Implantable Cardioverter Programming and Testing[11] is based on the outcome of trials performed to reduce inappropriate shocks in primary prevention patients. This Consensus Statement includes information on optimal ICD programming for primary prevention patients, and the purpose is to provide evidence based expert guidance. The

recommendation for primary prevention ICD patients was to program the slowest tachycardia therapy zone limit between 185 and 200 bpm, or higher for younger patients. These findings and recommendations are consistent with the protocol required Conditional Shock Zone programming of 200 bpm.

19 Safety Reporting

Only events as described below are reportable. For the purpose of this study the EMBLEM™ S-ICD System will be referred to as the study device. Reporting starts from the date of informed consent. Refer to Section 18 for the known risks associated with the study device(s).

Reportable events are defined as:

- All device and/or procedure related adverse events regardless whether considered serious or not
- Device deficiencies
- Serious adverse events regardless of cause
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the physician's manual
    - Note 1: Planned hospitalizations for pre-existing conditions prior to enrollment are not considered a serious adverse event
    - Note 2: Procedures required by the clinical investigational plan without serious deterioration in health are not considered a serious adverse event

Death should not be recorded as an adverse event. Death should be recorded as an outcome of only one (1) serious adverse event.

Adverse event definitions provided below in Table 19-1 are based on ISO 14155:2011 and MEDDEV 2.7/3 (2015).

Table 19-1: Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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. 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 14155-2011*	Adverse event related to the use of a study device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the

Table 19-1: Event Definitions

Term	Definition
Ref: MEDDEV 2.7/3 (2015)	implantation, the installation, the operation, or any malfunction of the study device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the study device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or 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 serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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. **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 14155-2011*	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.

Table 19-1: Event Definitions

Term	Definition
Ref: MEDDEV 2.7/3 (2015)	
In addition, the following definitions and classifications are used: *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	
Observation	Adverse event that was transient or reversible and corrected with non-invasive interventions, such as reprogramming or oral medications, or was resolved with no intervention or monitoring Note: Invasive procedures that are purely diagnostic in nature should not be considered as a complication. Examples of procedures that are invasive, but not considered to be an intervention (observation), include: • Blood draw for laboratory analysis • Cardiac catheterization in which pressures are recorded, but without therapeutic interventions • Electrophysiology study to map arrhythmias, but without therapeutic intervention • Transesophageal echo (TEE) • Electrical (external) Cardioversion with IV sedation (the IV sedation used is for patient comfort and not part of the treatment)
Complication	Adverse event that resulted in: Death, serious injury, correction using invasive intervention, or permanent loss of device function. Note: Treatment delivered by cutting or piercing the skin or placing an instrument in a body cavity to provide therapy, include: • Surgical revision of an electrode • Electrophysiology study in which an ablation is performed • Angiogram in which angioplasty or stent placement is performed • Intravenous medications • Blood transfusions
Type I[1]	Related to the study device, procedure, therapy, or procedure related to the implant of the study device.
Type II	Related to protocol or procedures. Specifically related to protocol testing that is not patient standard of care.
Type III	Related to commercially available implanted components or commercially available features of the study device, or the procedure of a commercially available device
Type IV	Related to a change in the patient's condition or to therapies other than delivered by the implanted system.
Type V	Comments Only.

Table 19-1: Event Definitions

Term	Definition
Type VI	Exact duplicate of an AE with no change in content from a previously reported AE.

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

[1]Not to confound type III complications related to commercially available implanted devices other than the Emblem™ S-ICD system, all events related to the Emblem™ S-ICD system including events related to the required procedures will be coded Type I in the UNTOUCHED study. The implanted system as a whole is considered to be the study device.

19.1 *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 19-2.

Table 19-2. Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Not Related	Reporting 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; - 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.

Table 19-2. Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
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; - 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.

19.2 *Investigator Reporting Requirements*

Investigators shall report:

- Any **device and/or procedure related** adverse event whether considered serious or non-serious
    - All events reporting chest pain shall be reported. The device shall be reviewed for potential episodes of syncope or arrhythmias to determine if the incident was potentially related to a cardiovascular event.
- Any **protocol related** adverse event whether considered serious or non-serious
- Any serious adverse event
    - Includes serious adverse events related to conditions that existed at enrollment and worsened considerably.
- Any device deficiency (See Section 19.3)

Notes:

- Underlying diseases are not to be reported as AEs unless there is an increase in severity or frequency during the course of the investigation and the AE meets the reporting criteria outlined above. For centers in Austria cancer must always be reported as a Serious Adverse Event. Death should not be recorded

as an AE, but should only be reflected as an outcome of a specific SAE (see Table 19 1 for AE definitions), except in cases where the cause is unknown.

- Invasive procedures may occur that are not strictly interventional and done for medical convenience rather than medical necessity. These are not considered to be an adverse event since they are not related to an undesirable clinical outcome. Examples include:
  - Foley catheter placed in anticipation of a prolonged procedure
  - Intravenous fluids or medications related to a diagnostic procedure

19.3 *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. If any part of the implantable S-ICD system is explanted, the device(s) should be returned to BSC for analysis. Instructions for returning the study device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. 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 to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded 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 serious adverse event.

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
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.
Serious Adverse Event including Serious Adverse Device Effects and Deaths	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 per BSC request	• When documentation is available
Adverse Event – if system or procedure related	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution,	• Within **10 business days** after becoming aware of the information

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
	assessment of seriousness and relationship to the device.	• Reporting required until end of study.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency CRF with all available new and updated information.	• **Within 2 business days** of first becoming aware of the event and as per local/regional regulations. • Reporting required through the end of the study

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

19.4 *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating 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.

19.5 *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within two working 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 IPG should be interrogated. Investigational leads and related Boston Scientific CRM system components (e.g., IPGs) should be removed intact and returned promptly to Boston Scientific CRM for analysis.

20 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any study-required procedure 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 approved by BSC or it's delegate (e.g. CRO), the center'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 center's IRB/EC. Any modification requires approval 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 center 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,
- inform that source data might be transferred to the US without disclosing the subject identifiers
- mention study registration at ClinicalTrials.gov
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject and by the investigator and/or an authorized designee responsible for conducting the informed consent process. The original signed ICF will be retained by the center 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. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

21 Committees

21.1 *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of physicians with pertinent expertise that reviews and adjudicates key endpoint related events reported by study investigators.

Committee membership will include experts with the necessary therapeutic area and subject matter expertise to adjudicate all spontaneous shock episodes. The CEC will adjudicate all shocks given in the reported episodes, and will classify each shock as appropriate or inappropriate. Specific CEC responsibilities, qualifications, membership, and committee procedures will be outlined in a CEC charter.

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 production 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 UNTOUCHED Study may discontinue participation in the study or withdraw 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 centers 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 an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all study related documents and study related material provided by Boston Scientific to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.5 *Criteria for Suspending/Terminating a Study Center*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after center initiation, or if the center 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 center will continue to be followed according to the standard of care. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the study center otherwise.

23 Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, 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. In accordance with the Corporate Policy for the Conduct of Human Subject Research, 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 *Subject Reimbursement*

No subject reimbursement will be provided for this standard of care study.

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26 Abbreviations and Definitions

26.1 *Abbreviations*

Abbreviations are shown in Table 26-1.

Table 26-1: Abbreviations

Abbreviation/Acronym	Term
bpm	beats per minute
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRF	Case Report Form

Table 26-1: Abbreviations

Abbreviation/Acronym	Term
EC	Ethics Committee
ECG	Electrocardiogram
EIT	Electrode Insertion Tool
FCC	Federal Communications Commission
ERI	Elective Replacement Indicator
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICD	Implantable Defibrillator
ICF	Informed Consent Form
IDE	Investigational device exemption
IRB	Institutional Review Board
J	Joules
LVEF	Left Ventricular Ejection Fraction
ms	Millisecond
N/A	Not Applicable
NNT	Number Needed to Treat
NR	Not Required
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
OUS	Outside the United States
PCMCIA	Personal Computer Memory Card International Association
PCr	Serum (Plasma) Creatinine Level
PMA	Premarket Approval
ppm	pulses per minute
RF	Radio Frequency
SAS	Statistical Analysis System
Spontaneous Episode	Any arrhythmia that is stored by the EMBLEM pulse generator
SVT	Supraventricular Tachycardia
EMBLEM™ S-ICD System	The BSC subcutaneous defibrillator, including the EMBLEM Pulse Generator, Subcutaneous Electrode, Programmer, and Electrode Insertion Tool (EIT)
TV-ICD	Transvenous ICD
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
VT/VF Storm	3 or more treated VT/VF episodes occurring within 24 hours

26.2 *Definitions*

Terms are defined in Table 26-2.

Table 26-2: Definitions

Term	Definition

Inappropriate Shock	Any shock given in an episode for a rhythm other than ventricular arrhythmia. This includes shocks after an appropriate shock for ventricular arrhythmias in the same episode.
Normal Battery Depletion	A pulse generator that is not associated with a complaint and has reached its elective replacement indicator(s) with implant time that meets or exceeds the nominal (50th percentile) predicted longevity at default (labeled) programmable settings OR with implant time exceeding 75% of the expected longevity using the longevity calculation tool available at time of product introduction, calculated using the device's actual use conditions and programmable settings
Permanent Loss of Device Function	Refers to: 1) the permanent loss of shock therapy and/or post shock pacing; 2) permanent loss of appropriate sensing in all available sensing configurations (oversensing that results in persistent inappropriate shocks or undersensing that could lead to undetected arrhythmias). Loss of device function includes programming the PG permanently off or temporarily off in advance of an explant/revision.