Boston Scientific

Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD

The EFFORTLESS S-ICD Registry

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Protocol History

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Initial Release	August 06, 2010	• Initial Version (limited submission)
Amendment	August 30, 2010	• Removed ≥ 18yrs exclusion criteria
Amendment	November 10, 2013	• Sponsorship moved to Boston Scientific (CRM Division)
Amendment	May 04, 2017	• Updated Front Page, Protocol History table, Contact Information and Table of Contents • Correction of typing errors • Replacement of specific model names by generic names document in order to reflect new S-ICD generations • Updated expected Registry duration according to actual enrolment numbers • Added Sub-Study information and deleted sponsor information in Protocol Summary Table • Deleted all references to IRB and FDA • Clarification of clinical event adjudication • Added reference to the Sub-Study (Appendix E) to the purpose and objective, statistical method and risk section • Clarification of retention of source data • Added requirement of Final Summary report collection for the Annual Follow-up • Clarification of Follow-up window for the Annual Follow-up • Clarification added how to handle patients, who had an S-ICD component replaced or explanted • Updated "Potential Risk and Benefit" section to reflect the updated S-ICD risk profile • Clarification of potential benefits for the patient • Updated the "Role of Boston Scientific Representatives" section • Added investigator responsibility to sign eCRFs • Clarification added how new information shall be shared with patients • Updated Appendix A with new S-ICD product information • Updated Acronym table and literature references • Updated Protocol Signature Page • Description of the Extension Sub-Study added as Appendix E

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SUMMARY OF EFFORTLESS S-ICD Registry

Introduction:	The S-ICD Subcutaneous Implantable Cardioverter Defibrillator (S-ICD®; Boston Scientific) is a novel implantable defibrillator that does not require any electrodes to be placed in or on, the heart. By using anatomical markers, the S-ICD system can be implanted without the need for any imaging system and also has an entirely subcutaneous sensing and defibrillation electrode. Together with algorithmic rhythm discrimination that uses a combination of rate and morphology criteria derived from its surface-equivalent ECG, these properties suggest that the S-ICD should have a lower incidence of associated complications, including inappropriate therapies, compared to standard transvenous ICD systems.
Overview:	The Evaluation of Factors Affecting Clinical Outcome and Cost Effectiveness of the S-ICD or "EFFORTLESS S-ICD" Registry, is designed to document early, mid- and long-term clinical and cost effectiveness outcomes associated with the implantation of the S-ICD pulse generator and subcutaneous electrode. Data will be collected to evaluate perioperative (30 days post implant) and mid-term (minimum 360 days post implant) clinical complication rates associated with the S-ICD system. Long-term (up to 60 months) post implantation complication rates will also be reported and the patients' perception of their therapy will be evaluated using Quality of Life assessments. In addition to complication rates associated with the S-ICD system, data will also be collected to evaluate the percentage of inappropriate shocks delivered for atrial fibrillation (AF) and/or superventricular tachycardias (SVT). The Registry will include an exploratory analysis of resource utilization and costs based on measures of clinical outcome such as complication rates, unscheduled hospitalizations and length of stay. The objective will be to enable comparison of costs of the S-ICD system versus a standard transvenous system. The Sub-Study will extend the EFFORTLESS S-ICD Registry in order to collect long-term follow-up data of the EFFORTLESS S-ICD patients to achieve an average of approximately 8 years of follow-up from index procedure. The purpose of the Sub-Study is to document the reason for S-ICD system replacements or revisions and describe the associated clinical events and outcomes. The Registry will be conducted in accordance with the Declaration of Helsinki, ISO 14155:2009 and all applicable local and national regulations.
Design:	EFFORTLESS S-ICD is an observational, prospective, non-randomized Registry that will be conducted at approximately 50 clinical centres worldwide. Approximately 1000 patients implanted with, or meeting eligibility criteria for the implantation of the S-ICD system will be enrolled and followed per standard of care for up to 60 months post implant.
Primary Objective:	To demonstrate the early, mid- and long-term clinical outcome of the S-ICD system.
Registry Endpoints	• Perioperative (30 days post implant) Complication-Free Rate • 360-day Complication-Free Rate • Percentage of Inappropriate Shocks for AF/SVT
Observational Data Collection	• Clinical Indications for implant • Patient demographics • Type of anesthesia/analgesia • Implant procedure duration • Use of fluoroscopy and X-Ray • Shock conversion efficacies (spontaneous & induced) • All cause therapies (appropriate & inappropriate) • Overall complication rates with time • Frequency of scheduled/unscheduled follow-ups/hospitalizations • All cause mortality • Length of hospital stay (implant procedure and follow-ups) • All clinical events • Clinical event rates over time • Quality of Life

	• Total shock burden	• Hospital personnel implant and follow-up experience (using surveys)
Sample Size:	The target sample size is approximately 1000 patients.	
Registry Duration:	The expected duration, from enrolment to closure of the main Registry, will be approximately 108 months.	
Patient Selection:	Patients from the investigators' general implantable cardioverter-defibrillator (ICD) patient population will be eligible to be enrolled in this Registry. Patients should meet all the inclusion criteria and none of the exclusion criteria. Retrospective enrolments are allowed providing minimal data requirements are met.	
Inclusion Criteria:	Patients who meet the following criteria should be given consideration for inclusion in the Registry: 1. Eligible for implantation of an S-ICD system per local clinical guidelines or currently implanted with an S-ICD system (SW version 1.59.0 or later*) 2. Willing and able to provide written informed consent or have informed consent as provided by a legal representative **Patients currently implanted must meet minimal dataset requirements to be enrolled as described in the Registry Protocol*	
Exclusion Criteria:	Patients who meet any one of the following criteria must be excluded from the Registry: 1. Participation in any other investigational study that may interfere with interpretation of the Registry results 2. Incessant ventricular tachycardia and/or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing 3. Patients with unipolar pacemakers or implanted devices that revert to unipolar pacing	
Extension Phase Sub-Study (Appendix E)	The Sub-Study will extend the EFFORTLESS S-ICD Registry in order to achieve an average of approximately 8 years of follow-up from index procedure. The expected duration of the extension phase is approximately 72 month. A subgroup of approximately 200 patients will be enrolled in the Sub-Study at a sub-set of EFFORTLESS S-ICD sites. These patients will be followed once annually for additional 5 years in the EFFORTLESS S-ICD Registry from the time of consent into the Extension Phase. The following data will be analysed in addition of the main study endpoints: <u>Primary Analysis</u> • Rate of long-term S-ICD system-related adverse events • S-ICD replacements for functionality (e.g. pacing, CRT, ATP etc.) • Device longevity <u>Secondary Analysis</u> • Rate of electrode failures and revisions, including the reason for revision • Rate of device failures and revisions, including the reason for revision • Rate of complications related to the S-ICD replacements • Appropriate therapy for VT/VF • Inappropriate shock therapy (e.g. atrial fibrillation, supraventricular tachycardia) The In- and Exclusion Criteria for the Sub-Study are the following: <u>Inclusion Criteria</u> 1. Subjects who are actively enrolled in the EFFORTLESS S-ICD Registry OR Subjects who completed the 5-year follow-up in the EFFORTLESS S-ICD study.	

	All clinical events, spontaneous and induced episode data and system replacement or revision data since the last EFFORTLESS S-ICD Annual Follow-Up of the main study must be available in medical files or equivalent. 2. Subjects who are actively implanted with an S-ICD pulse generator (SQ-RX, EMBLEM or EMBLEM MRI) and an S-ICD electrode (Q-TRAK or EMBLEM) or any other future commercial available versions 3. Willing and able to provide written informed consent or have informed consent as provided by a legal representative and willing to participate in all testing and follow-ups as described the Sub-Study protocol 4. Age 18 or above, and of legal age to give informed consent specific to national laws <u>Exclusion Criteria</u> 1. Subjects with device replacement from the S-ICD to a transvenous ICD 2. Subjects with unipolar pacemakers or implanted devices that revert to unipolar pacing 3. Subjects that are participating in any other investigational study that may interfere with interpretation of the Registry results, without the written approval of Boston Scientific

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1.0 Introduction

1.1 Sudden Cardiac Death and ICD Therapy

Sudden Cardiac Death (SCD) occurs in approximately 50,000-70,000 patients annually in the UK, proportionate numbers of patients in other European countries and more than 350,000 patients in the USA[1]. SCD is responsible for the highest number of deaths attributable to coronary heart disease and is defined as death from cardiac causes occurring unexpectedly within 1hr of onset of symptoms. 85-90% of SCD episodes are related to a first recognized arrhythmic event. Treatments for SCD are generally categorized into either primary or secondary with primary prevention strategies aimed at preventing the first life-threatening arrhythmic event and secondary aimed at preventing death from recurrent events.

It is generally accepted that implantable cardioverter defibrillators (ICDs) have demonstrable benefit in patients implanted for secondary prevention reasons (i.e. those that have survived an episode of cardiac arrest, have spontaneous VT causing syncope or significant hemodynamic compromise or documented VT and an ejection fraction of ≤ 35%). There is also significant evidence that prophylactic implantation of ICDs for primary prevention reduces overall mortality in subsets of patients. [2, 3,4] However, in many geographies, there remains a question of cost-effectiveness for ICD therapy in this primary prevention population. This is particularly true in light of the high incidence of post-implant complications which can add significant financial burden[5].

1.2 Transvenous ICD Complications

A large proportion of the complications associated with ICD therapy are related to the leads that are implanted in or on the heart, for sensing and defibrillation. In conventional transvenous ICD systems, one or two leads are required to be implanted into the heart or associated vessels, often through a venous access. The implantation of such leads, by definition, runs the risk of specific clinical complications such as pericardial effusion/tamponade, perforation and pneumothorax. In addition, repositioning of leads in the event of dislodgement, fracture or other associated mechanical event has an associated risk. In a recent report on the outcome of approximately 31,000 Medicare beneficiaries who underwent ICD implantation between October 2002 and September 2003, 11% experienced one or more early complications with the largest percentage of events being related to mechanical complication of the ICD system[6]. In smaller studies, overall complication rates have been reported to be as high as 30% after approximately 4 years of follow-up with lead -related complication rates accounting for 15% of events[7]. Subsequent, single centre experience data from Borleffs et al[8] and Kleeman et al[9] indicate that lead failure rates can be as high as 20-40% over 8-10 years of follow-up and complication rates may also be higher in the pediatric ICD population where long term (5-12yrs) reports, suggest rates of 40% or higher[10,11].

While an ICD is designed to provide shock treatment for potential life threatening, malignant, ventricular arrhythmias (VT/VF), the actual delivery of shock therapy has been shown to have a negative impact on Quality of Life measures. In the Canadian Implantable Defibrillator Study (CIDS) Irvine et al., (2002)[12] reported that while emotional and physical health scores were improved in patients in the ICD group compared to the amiodarone group, this was not the case in those patients that had received more than five shocks. Similarly, Schon et al., (2002)[13] demonstrated that in

patients from the Antiarrhythmic Versus Implantable Defibrillators (AVID) trial, the occurrence of ICD shocks was associated with decreased physical and mental well-being and with increased patient concerns. While it is unclear as to whether shocks are the major determinant of poor QOL outcomes in all ICD patients, it can be agreed that it is important to ensure that shocks are delivered only when truly necessary[15]. Unfortunately there is still a high incidence of inappropriate therapy associated with transvenous ICDs, where a shock is delivered for reasons other than a malignant VT/VF episode. The most common cause of inappropriate therapy is misclassification of atrial fibrillation (AF) or supraventricular tachycardias (SVT) but there are also well documented incidences of inappropriate therapy due to oversensing of muscle myopotentials, T waves, Electromagnetic Interference (EMI) and noise due to lead or other mechanical failures. Unfortunately, for transvenous systems which rely primarily on intracardiac electrograms to distinguish cardiac signals, discriminating an atrial driven arrhythmia from a ventricular event can prove challenging and despite increasingly sophisticated algorithms, the incidence of inappropriate therapy is still reported to occur in close to 10% of implanted patients[15].

1.3 Costs and Cost Effectiveness of ICD Therapy

As stated above, ICD therapy has demonstrable benefit in terms of survival in both primary and secondary indicated patient populations; however the cost effectiveness of the therapy has been challenged. In the study by Reynolds et al[6] following more than 30,000 Medicare patients implanted with ICDs, the associated cost of any complication was calculated at nearly $7,500 per patient. The authors conclude that if 100,000 ICDs were implanted in a year, the incremental cost to Medicare associated with the complications would exceed $78 million. Since the most current data from the US ICD registry suggests that more than 10,000 ICD implants were being recorded each month in 2008[16] the actual costs associated with transvenous complication rates will likely be even higher. A metanalysis of published ICD trial data by Groeneveld et al.[17] calculated that the follow-up costs associated with implantation of an ICD ranged from $5,000-$17,000 per year depending on the clinical data evaluated. These costs have direct impact on the availability of ICD therapy in countries with managed healthcare. A review of the effects and costs of ICD therapy in 2006 as a Health Technology Assessment[18] subsequently referenced by the National Institute for Clinical Excellence (NICE) in the UK to justify not approving reimbursement for all primary prevention ICD indications states:

"*The evidence of short to medium term patient benefit from ICDs is strong but cost effectiveness modeling indicates that the extent of that benefit is probably not sufficient to make the technology cost effective….in the UK. One reason is the high rates of post implantation hospitalization. Better patient targeting and efforts to reduce the need for such hospitalization may improve cost effectiveness*".

It should be noted that both these analyses were completed prior to 2007 and therefore do not fully reflect the potential added burden of recent industry recalls which are anticipated to have impacted more than 250,000 patients worldwide[19]. In light of these data, it is clear that an ICD system with a demonstrable reduction in overall complication rates may also significantly improve the follow-up cost associated with ICD therapy. Such a system must be able to demonstrate a reduced incidence of mechanical complications-in particular with respect to lead related issues- but also a reduction in the incidence of inappropriate therapies for AF/SVT.

1.4 The Patients Perspective- Quality of Life

The importance of considering the patient's mental well-being in the relationship between SCD and implantation of any type of ICD should not be underestimated particularly in light of the fact that therapy (whether appropriate or inappropriate) is delivered in the form of a high energy shock. While the majority of ICD patients do well after receiving their device (considering it a life-saving companion rather than unwanted "shock box") between a quarter and a third do face psychological difficulties including chronic anxiety and depression [20,21]. Anxiety associated with the implantation of an ICD can have significant impact on a patients' lifestyle and over all well-being. It is not unusual for an ICD patient to become sedentary after receiving their device in the belief that it will reduce their likelihood of receiving a shock. Unfortunately adopting such a lifestyle has a negative cyclic impact on long term health, particularly considering the importance of exercise in the recovery of cardiac patients as well as its well documented impact on perceived Quality of Life. In addition, it has also been shown that ICD patients who are anxious or depressed may actually be at higher risk of an arrhythmic event or even death[22,23,24]. Clearly therefore, understanding the patients' perspective through Quality of Life measures such as validated questionnaires (e.g. the ICD Patient Concerns Questionnaire), should be considered as standard indicators of clinical outcome when evaluating any new ICD technology, particularly if such evaluations are able to identify those patients who may be at risk of arrhythmic events. It should also be remembered that Quality of Life measures are key determinants in calculations of cost-effectiveness, allowing measures of Quality Adjusted Life Year outcomes or QALYs which are frequently used to evaluate the benefit of a new therapy over existing medical options[18]. For these reasons, along with device based measures of outcome such as clinical events and complications, the EFFORTLESS S-ICD Registry will also collect Quality of Life outcomes from prospective patients using a brief set of validated questionnaires. The data collected will be used to more fully understand the impact of the S-ICD from the patients' perspective. In addition, the responsible core lab has access to a large database of equivalent Quality of Life scores taken from transvenous ICD patients enrolled in the "Mood and Personality as Precipitants of Arrhythmia in Patients with an Implantable Defibrillator (MIDAS) study[20] allowing direct Quality of Life comparisons between S-ICD and transvenous ICD patients.

2.0 Background of the Subcutaneous ICD (S-ICD)

The feasibility of a subcutaneous ICD without the need for a transvenous lead system has been investigated and demonstrated through animal[25,26], research[27,28,] and acute and chronic human[29,30] studies. Recent data published in the New England Journal of Medicine[31], summarized the studies conducted to evaluate the most appropriate electrode placement and system configuration for a subcutaneous system as well as the required defibrillation threshold (DFT) energy for such a system. Within patient comparison of a permanent transvenous system and a temporary S-ICD system, reported that the average defibrillation threshold for the S-ICD system was 36.6±19.8J versus 11.1±8.5J for transvenous. As suspected, subcutaneous defibrillation requires greater energies; however, the DFT for the S-ICD system was within the realm that made subcutaneous defibrillation using an implanted pulse generator a reality[26,28,31,].

In addition to an acceptable defibrillation threshold, studies in small cohorts of patients have also demonstrated that the S-ICD system has a high level of sensitivity. In two studies where the S-ICD system was permanently implanted and tested, the

device successfully detected 100% of all VT/VF episodes, either induced at implant (n=155 episodes) or detected as spontaneous episodes in ambulatory settings (n=12 episodes)[31]. In a comparative study evaluating induced ventricular and atrial arrhythmias in transvenous (RA, RV Can +Coil) and S-ICD equivalent cutaneous electrode configurations, there was no difference in ventricular arrhythmia detection (100% S-ICD sensitivity versus 99.2% (range 97.7-100%) for single chamber transvenous configurations and 100% S-ICD sensitivity versus 98.4% (range 95.3-100%) for the dual chamber transvenous configurations). However, a significant difference was observed with specificity analysis where each system was tested to discriminate atrial arrhythmias and withhold shock therapy. In this case, the S-ICD configuration demonstrated 98.0% specificity versus 68.0% (range 42.0 – 92.0%) for the transvenous configurations. The majority of misclassifications by the transvenous systems were due to AF[32].

A notable difference between the S-ICD and transvenous systems is that the S-ICD system does not rely on near-field intracardiac signals for arrhythmia discrimination. Rather, the S-ICD system uses three subcutaneous sensing vectors with signal characteristics that closely resemble that of traditional surface ECG signals. The sensing performance of the S-ICD system is tested in both supine and standing patient positions prior to hospital discharge following implantation. This testing allows the S-ICD system to characterize any changes in S-ECG signal that may occur due to posture[33], thereby enabling the system to improve its automatic selection of the desired sensing vector. In addition, the system forms a reference ECG template in normal sinus rhythm for use during rhythm discrimination. By using a combination of criteria regarding rate and morphology of the surface equivalent ECG signal for rhythm discrimination, the S-ICD system may have a clear advantage over traditional transvenous systems for rhythm discrimination.

While speculative, these data do suggest that the S-ICD system may reduce the level of inappropriate therapies in patients experiencing atrial arrhythmias.

The EFFORTLESS S-ICD Registry is designed to evaluate whether implantation of a subcutaneous ICD can reduce the complication rate, the incidence of inappropriate therapy and the extrapolated costs associated with ICD therapy, versus a standard transvenous system.

2.1 System Description

The S-ICD System is an implantable defibrillator technology that treats ventricular tachyarrhythmias using a subcutaneous pulse generator and electrode system rather than a transvenous lead system. The system is CE marked (June 2009) and approved for distribution in the countries in which the Registry will be conducted.

The S-ICD System currently consists of four devices. Future generations of the devices will be included in the Registry, upon approval in their respective geography.

- S-ICD subcutaneous implantable defibrillator pulse generator;
- S-ICD subcutaneous electrode;
- Electrode insertion tool (EIT);
- S-ICD programmer.

In addition to these devices, the S-ICD System is designed to work with the following accessories:

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

A detailed description and the principle of operation for the S-ICD System and each system component are provided in Appendix A: Principle of Operation.

3.0 Purpose and Objectives

The purpose of the Evaluation of Factors Affecting Clinical Outcome and Cost Effectiveness of the S-ICD or "EFFORTLESS S-ICD" Registry, is to document early, mid-and long-term operational and clinical outcomes associated with the implantation of the Boston Scientific S-ICD system. The evaluation will include documenting the patients' perception of his/her therapy through Quality of Life (QOL) assessments. The study will be conducted at approximately 50 clinical centres worldwide in patients requiring an ICD for the treatment of ventricular tachyarrhythmias.

Data will be collected to evaluate perioperative (30 day post implant), mid- (360 day post implant) and long-term (up to 60 months) clinical complication rates associated with the implantation of the S-ICD system as well as the percentage of patients experiencing inappropriate shocks for AF and/or SVT. The Registry will also include analysis of resource utilization and costs based on measures of clinical outcome such as complication rates, unscheduled hospitalizations and length of stay. The objective will be to enable comparison of costs of the S-ICD system versus a standard transvenous system.

The Sub-Study (see Appendix E) will extend the EFFORTLESS S-ICD Registry in order to collect long-term follow-up data on a subset of EFFORTLESS patients to achieve an average of approximately 8 years of follow-up from index procedure.

The purpose of the Sub-Study is to document the reason for S-ICD system replacements or revisions and describe the associated clinical events and outcomes.

Data will be collected in conformance with the "Declaration of Helsinki", ISO 14155:2009 and the laws and regulations of the country in which the research is conducted.

3.1 Registry Objective

The objective of the EFFORTLESS S-ICD Registry is an observational, standard of care evaluation designed to demonstrate the early, mid and long-term clinical effectiveness the Boston Scientific S-ICD System. In addition, analysis of resource utilization and costs will be performed to document treatment costs for periods defined by Registry endpoints.

3.2 Registry Endpoints

The primary Registry endpoints will be examined using the following metrics:

- **Registry Endpoint 1**: Perioperative (30 days post implant) S-ICD System Complication Free Rate

- **Registry Endpoint 2**: 360 day S-ICD System Complication Free Rate
- **Registry Endpoint 3**: Percentage of Inappropriate Shocks for AF/SVT

3.2.1 Observational Data Collection

When available, descriptive statistics will be used to present observational data to further characterize the performance of the S-ICD system. This can include (but is not limited to):

- Clinical Indications for implant
- Patient demographics
- Type of anesthesia/analgesia
    - General anesthesia/local anesthesia/conscious sedation etc.
- Implant procedure duration
- Use of fluoroscopy and X-Ray
- Induced Shock Conversion Efficacy
    - Defined as any shock delivered by the S-ICD pulse generator that terminates the induced arrhythmia and does not require an external defibrillator.
- Spontaneous Shock Conversion Efficacy
    - Defined as any shock delivered by the S-ICD pulse generator that terminates the spontaneous arrhythmia (device defined end of episode)
- First Shock Conversion Efficacy
    - Defined as the percentage of successful conversions (device defined end of episode) caused by the first shock delivered by the S-ICD pulse generator. Data will be evaluated for both induced and spontaneous episodes
- All cause therapy (appropriate and inappropriate)
    - Inappropriate therapy is defined as delivery of shock therapy for any rhythm other than VT/VF.
- Total Shock Burden
    - Defined as the total number of therapies delivered (both appropriate and inappropriate) divided by the total number implanted patients
- Complication rates over time
- Frequency of scheduled and unscheduled follow-ups/hospitalizations
- All cause mortality
- Length of hospital stay
    - Where possible, hospital stay lengths will be calculated for implant procedure as well as scheduled and unscheduled follow-ups

- All clinical events
- Clinical event rates over time
- QOL Assessments
    - Patients will complete a brief set of standardized QOL questionnaires at baseline (pre-implant), 3 months post-implant, 6 months post-implant and 12-months post implant (see section 7.8) with the intention of comparing scores with a transvenous ICD cohort
- Hospital personnel implant and Follow-Up Experience (using an optional survey to be completed at two time points)

4.0 Registry Design

4.1 Overview

EFFORTLESS S-ICD is an observational, prospective, non-randomized, standard of care evaluation to be conducted at approximately 50 Investigational centres worldwide where the S-ICD is approved for use and distribution.

Approximately 1000 patients currently implanted with*, or meeting eligibility criteria for the implantation of, an S-ICD System may be enrolled in the Registry. Following implant, data will be collected from each patients' scheduled and unscheduled follow-ups for at least 360 days post implant per the standard of care follow-up schedule as defined by their clinical institution. Once the 360 days of follow-up have been completed for all enrolled patients, they will continue to be followed per institutional standard of care but data will then only be collected once annually for the next 48 months. This will ensure that at least 60 months' data is available post implant on system status and clinical events.

**Retrospective enrolments meet minimal dataset requirements as described in Section 5.9*

4.2 Registry Duration

The duration, from first enrolment to Registry closure, is expected to be approximately 108 months.

4.3 Scope of Registry and Follow-Up Schedule

Patients will be followed per standard of clinical care throughout the duration of the Registry. Data will be collected from implant and all scheduled and unscheduled follow-ups up until at least 360 days of follow-up has been recorded (usually from a 12 month post-implant follow-up or closest equivalent). Subsequently data will be collected once annually for the next 48 months to ensure that a total of 60 months data post implant, is available. All complications, hospitalizations and clinical events that occur between annual follow-ups will be reported. The actual follow-up schedule is defined by the standard of care at their clinical institution.

4.4 Clinical Events and Spontaneous Episodes

At a minimum, end-point-related clinical events and end-point-related spontaneous episode data will be reviewed and adjudicated.

5.0 Statistical Methods and Analysis

The statistical analyses related to this Registry including the Sub-Study (see Appendix E) will be executed by the Boston Scientific Clinical Department and/or consultants working on behalf of Boston Scientific. All patients enrolled in the Registry will be included in the analysis. As an observational non-randomized single arm evaluation, the statistical analyses will be descriptive.

5.1 Description of Baseline Variables

Baseline demographics and clinical variables, including but not limited to relevant descriptors from the medical history, risk factors, co-morbidities, and NYHA functional class for heart failure if available, will be summarized for the cohort of patients enrolled in this Registry. Continuous variables will be summarized as means, standard deviations, medians, minimums, maximum, and interquartile ranges. Categorical variables will be summarized as frequencies and percentages. A summary of the eligibility status of enrolled patients will be performed.

5.2 Procedural and In-Hospital Experience Endpoints

Outcomes related to the Boston Scientific S-ICD procedure such as, but not limited to, type of anesthesia, implant duration, use of fluoroscopy or X-ray and length of hospital stay will be summarized as described in section 5.1 based on the type of variable, continuous or categorical.

5.3 Registry Endpoints

- **Registry Endpoint 1**: 30-Day S-ICD Complication-Free Rate*, will be summarized as the number of subjects and the percentages relative to the Registry population including the corresponding 95.0% two-sided exact binomial confidence interval.
- **Registry Endpoint 2**: 360-Day S-ICD Complication-Free Rate*, will be analyzed using the Kaplan-Meier (KM) estimate and its corresponding 95.0% confidence interval based on Peto estimate of the standard error.
- **Registry Endpoint 3**: The Percentage of Inappropriate Shocks for AF/SVT, will be analyzed by dividing the number of patients who received at least one inappropriate shock over the total number implanted patients. The mean, median and inter-quartile follow-up time will also be presented.

**Type I Complications will be considered to count towards the complication rate endpoints (see section 10.2). Events related to normal device function e.g. battery deletion within acceptable margins, will not count against the endpoints*

5.4 Quality of Life Analysis

Both between and within group analyses will be performed. Between group analyses will compare the QOL scores recorded from the EFFORTLESS S-ICD cohort with the MIDAS cohort of transvenous patients using a mixed model approach with repeated measures. Within group analyses will examine determinants of poor Quality of Life within the S-ICD cohort. All analyses will be performed using both a univariable and multivariable approach. Multivariable analysis provides the potential to adjust for factors that may impinge on the relationship between the independent variable and the dependent variable (endpoint).

5.5 Additional Data Analysis

- Conversion efficacies for both induced and spontaneous episodes and first shock will be summarized as the number of subjects and the percentages relative to the Registry population including the corresponding 95.0% two-sided exact binomial confidence interval.
- Clinical event rates will be presented as 30-day event rates as summarized by number of subjects and its corresponding percentage and 95.0% two-sided exact binomial confidence interval and long-term rates as either linear rates or Kaplan-Meier freedom from event.
- Linearised rate of inappropriate therapies will also be calculated by dividing the total number of inappropriate therapies by the total number of follow-up patient years. Linearised rate calculation will only be initiated if a minimum of 100 patient years have been reached.
- Kaplan-Meier estimates and curves for therapy delivered including:
  - Time to first therapy delivered (both appropriate and inappropriate)
  - Time to first appropriate therapy delivered
  - Time to first inappropriate therapy delivered
- Re-occurrence of inappropriate shock therapy after reprogramming will be calculated using the total number of additional inappropriate shocks recorded from patients who have previously experienced at least one inappropriate shock and had their S-ICD reprogrammed in an attempt to resolve the issue (adjustments may include but are not limited to, changing sensing vector, adjustment to ECG gain, reprogramming of shock rates)
- Considering that patients who are prospectively enrolled in this Registry will come from the investigator's general ICD population, it is a priori unknown how many will be primary versus secondary prevention patients. Analyses will be conducted for primary versus secondary prevention, for inclusion in separate cost-effectiveness models for those populations.

5.6 Sample Size Determination

As part of an observational Registry, the target sample size of 1000 was not derived through a power driven hypothesis testing. Tables 1 & 2 below demonstrate the corresponding confidence interval length for estimated values for Registry Endpoints 1 and 2 at various sample size time points. The maximum sample size presented is 900 to allow up to 10% attrition rate.

Table 1: 30-Day Complication Free Rate Estimated Values & 95.0% Exact Conf. Interval

	Sample Size								
Estimated Value	100	200	300	400	500	600	700	800	900
90%	-7.6%/+5.1%	-5.0%/+3.8%	-4.0%/+3.2%	-3.4%/+2.8%	-3.0%/+2.5%	-2.7%/+2.3%	-2.5%/+2.1%	-2.3%/+2.0%	-2.1%/+1.9%
91%	-7.4%/+4.8%	-4.9%/+3.6%	-3.8%/+3.0%	-3.2%/+2.6%	-2.9%/+2.4%	-2.6%/+2.2%	-2.4%/+2.0%	-2.2%/+1.9%	-2.1%/+1.8%
92%	-7.2%/+4.5%	-4.7%/+3.4%	-3.7%/+2.8%	-3.1%/+2.5%	-2.7%/+2.2%	-2.5%/+2.0%	-2.3%/+1.9%	-2.1%/+1.8%	-2.0%/+1.7%
93%	-6.9%/+4.1%	-4.5%/+3.1%	-3.5%/+2.6%	-3.0%/+2.3%	-2.6%/+2.1%	-2.3%/+1.9%	-2.1%/+1.8%	-2.0%/+1.7%	-1.9%/+1.6%
94%	-6.6%/+3.8%	-4.2%/+2.9%	-3.3%/+2.4%	-2.8%/+2.1%	-2.5%/+1.9%	-2.2%/+1.8%	-2.0%/+1.6%	-1.9%/+1.5%	-1.8%/+1.5%
95%	-6.3%/+3.4%	-4.0%/+2.6%	-3.1%/+2.2%	-2.6%/+1.9%	-2.3%/+1.7%	-2.1%/+1.6%	-1.9%/+1.5%	-1.7%/+1.4%	-1.6%/+1.3%
96%	-5.9%/+2.9%	-3.7%/+2.3%	-2.9%/+1.9%	-2.4%/+1.7%	-2.1%/+1.5%	-1.9%/+1.4%	-1.7%/+1.3%	-1.6%/+1.2%	-1.5%/+1.2%
97%	-5.5%/+2.4%	-3.4%/+1.9%	-2.6%/+1.6%	-2.2%/+1.4%	-1.9%/+1.3%	-1.7%/+1.2%	-1.5%/+1.1%	-1.4%/+1.1%	-1.3%/+1.0%
98%	-5.0%/+1.8%	-3.0%/+1.5%	-2.3%/+1.3%	-1.9%/+1.1%	-1.6%/+1.0%	-1.5%/+1.0%	-1.3%/+0.9%	-1.2%/+0.9%	-1.1%/+0.8%
99%	-4.4%/+1.0%	-2.6%/+0.9%	-1.9%/+0.8%	-1.5%/+0.7%	-1.3%/+0.7%	-1.2%/+0.6%	-1.0%/+0.6%	-1.0%/+0.6%	-0.9%/+0.5%

Exact confidence interval based on the mathematical relationship between the F distribution and cumulative binomial distribution (Fleiss et al (2003)), Statistical Methods for Rate and Proportion, 3rd Edition

Table 2: 360-Day Complication Free Rate Estimated Values & 95.0% KM Conf. Inter. (Peto)

	Sample Size								
Estimated Value	100	200	300	400	500	600	700	800	900
70%	± 9.0%	± 6.4%	± 5.2%	± 4.5%	± 4.0%	± 3.7%	± 3.4%	± 3.2%	± 3.0%
71%	± 8.9%	± 6.3%	± 5.1%	± 4.4%	± 4.0%	± 3.6%	± 3.4%	± 3.1%	± 3.0%
72%	± 8.8%	± 6.2%	± 5.1%	± 4.4%	± 3.9%	± 3.6%	± 3.3%	± 3.1%	± 2.9%
73%	± 8.7%	± 6.2%	± 5.0%	± 4.4%	± 3.9%	± 3.6%	± 3.3%	± 3.1%	± 2.9%
74%	± 8.6%	± 6.1%	± 5.0%	± 4.3%	± 3.8%	± 3.5%	± 3.2%	± 3.0%	± 2.9%
75%	± 8.5%	± 6.0%	± 4.9%	± 4.2%	± 3.8%	± 3.5%	± 3.2%	± 3.0%	± 2.8%
76%	± 8.4%	± 5.9%	± 4.8%	± 4.2%	± 3.7%	± 3.4%	± 3.2%	± 3.0%	± 2.8%
77%	± 8.2%	± 5.8%	± 4.8%	± 4.1%	± 3.7%	± 3.4%	± 3.1%	± 2.9%	± 2.7%
78%	± 8.1%	± 5.7%	± 4.7%	± 4.1%	± 3.6%	± 3.3%	± 3.1%	± 2.9%	± 2.7%
79%	± 8.0%	± 5.6%	± 4.6%	± 4.0%	± 3.6%	± 3.3%	± 3.0%	± 2.8%	± 2.7%
80%	± 7.8%	± 5.5%	± 4.5%	± 3.9%	± 3.5%	± 3.2%	± 3.0%	± 2.8%	± 2.6%
81%	± 7.7%	± 5.4%	± 4.4%	± 3.8%	± 3.4%	± 3.1%	± 2.9%	± 2.7%	± 2.6%
82%	± 7.5%	± 5.3%	± 4.3%	± 3.8%	± 3.4%	± 3.1%	± 2.8%	± 2.7%	± 2.5%
83%	± 7.4%	± 5.2%	± 4.3%	± 3.7%	± 3.3%	± 3.0%	± 2.8%	± 2.6%	± 2.5%
84%	± 7.2%	± 5.1%	± 4.1%	± 3.6%	± 3.2%	± 2.9%	± 2.7%	± 2.5%	± 2.4%
85%	± 7.0%	± 4.9%	± 4.0%	± 3.5%	± 3.1%	± 2.9%	± 2.6%	± 2.5%	± 2.3%
86%	± 6.8%	± 4.8%	± 3.9%	± 3.4%	± 3.0%	± 2.8%	± 2.6%	± 2.4%	± 2.3%
87%	± 6.6%	± 4.7%	± 3.8%	± 3.3%	± 2.9%	± 2.7%	± 2.5%	± 2.3%	± 2.2%
88%	± 6.4%	± 4.5%	± 3.7%	± 3.2%	± 2.8%	± 2.6%	± 2.4%	± 2.3%	± 2.1%
89%	± 6.1%	± 4.3%	± 3.5%	± 3.1%	± 2.7%	± 2.5%	± 2.3%	± 2.2%	± 2.0%
90%	± 5.9%	± 4.2%	± 3.4%	± 2.9%	± 2.6%	± 2.4%	± 2.2%	± 2.1%	± 2.0%

Kaplan-Meier estimate confidence interval based on the Peto estimate of the standard error (Chernick, et al (2003)), Introductory Biostatistics for Health Sciences: Modern Applications Including Bootstrap.1st Edition

5.7 Missing Data

Every effort will be utilized to minimize missing data. The number of data for each variable presented will be stated. The number of patients withdrawing from the Registry will be presented with their corresponding time of discontinuation. Time-to-event drop-outs will be censored, consistent with the Kaplan-Meier approach. Any data outside follow-up time period tolerance that was used for analysis will be noted with results presented.

5.8 Other Statistical Considerations

Confidence intervals and statistical tests if applied will be performed at a two-sided 5% significance level unless specified otherwise. All p-values will be rounded to three decimal places. If opportunities should arise, data mining and modelling analyses of the Registry database would be utilized for publication and/or medical conference presentation purposes as long as the integrity and objectives of the Registry are not compromised.

5.9 Retrospective Enrolment Minimal Dataset Requirements

The Registry protocol does allow for the retrospective enrolment of patients already implanted with a Boston Scientific S-ICD system. There are some specific criteria associated with these enrolments that must be fulfilled prior to the enrolment of a retrospective patient:

- The patient meets all the inclusion criteria and none of the exclusion criteria as listed in sections 6.1.1 and 6.1.2
- The patient must be a commercial patient, i.e. they have been implanted with the S-ICD system since the CE mark approval of the device (June 2009).
- The patient has been implanted with a device initially equipped with SW version 1.59.0 or later
- Details of all clinical events (including death as necessary) and all spontaneous episodes that received therapy since implant, are available in medical files or equivalent
- Details of all system related clinical events/hospitalizations and deaths since implant are available in medical files or equivalent

6.0 Patient Population

6.1 Eligibility

Patients selected for participation in this Registry should be from the investigator's general ICD population. Data will be collected indicating if a patient receives the S-ICD for primary versus secondary prevention of SCD. Each investigator is responsible for screening all patients and selecting those who are appropriate for inclusion. Patients enrolled in the Registry must meet all inclusion criteria and none of the exclusion criteria as described below.

6.1.1 Inclusion Criteria

Patients who meet all of the following criteria may be considered for inclusion:

- Eligible for implantation of an S-ICD system per local clinical guidelines or currently implanted with an S-ICD system (SW version 1.59.0 or later*)
- Willing and able to provide written informed consent or have informed consent as provided by a legal representative

**Patients currently implanted must meet minimal dataset requirements to be enrolled as described in Section 5.9*

6.1.2 Exclusion Criteria

Patients who meet any one of the following criteria must be excluded:

- Participation in any other investigational study that may interfere with interpretation of the Registry results
- Incessant ventricular tachycardia (VT) and/or documented spontaneous, frequently recurring VT that is reliably terminated with anti-tachycardia pacing
- Patients with unipolar pacemakers or implanted devices that revert to unipolar pacing

7.0 Methods

7.1 Visit Schedule

Table 3 documents the information that will be requested at each visit.

Table 3: Summary of Information Requested at Each Follow-Up

	Enrolment	Implant	Scheduled FU	Unscheduled FU	Annual FU
Informed Consent	x				
Demographics & Medical History	x		x	x	
VT/VF Defibrillation Testing		x[A]	x[A]	x[A]	
Induced Episodes		x[A]	x[A]	x[A]	x[A]
Spontaneous Episodes		x	x	x	x
Clinical Events & Hospitalizations		x	x	x	x
Deaths	x	x	x	x	x
Withdrawals	x	x	x	x	x
Adverse Events	x	x	x	x	x

[A] If done

7.2 Enrolment

Patients may not be enrolled in the Registry until the investigator receives "Approval to Enrol" from the sponsor. Patients are considered enrolled after providing written informed consent in accordance with applicable local and national guidelines and/or Ethics Committee (EC) requirements.

7.2.1 Enrolment Data

Patient demographics, including age, height, weight, medical history, cardiovascular disease diagnoses and device indications will be collected for all enrolled patients. A pre-operative screening ECG for prospective patients should also be available. Table 4 lists the data that will be requested at the Enrolment visit.

Table 4: Enrolment Data Collection

Data Collection	Retention of Originals
Patient Consent Form Demographics (Physical) and Medical History including cardiac medications	Investigational Centre
Pre-operative ECG screening	Investigational Centre and e-Copy to Boston Scientific, if requested

7.3 Implant

7.3.1 Implant Procedure

The clinical investigator is responsible for implanting, testing, and programming the S-ICD System and using the standard of care methods established by the investigational centre (e.g. sterile technique, personnel required, etc.). Refer to the S-ICD System User's Manual for detailed instructions regarding the implantation and use of the S-ICD System.

7.3.2 Acute Defibrillation Testing

After implanting the S-ICD System, a ventricular arrhythmia can be induced using the S-ICD pulse generator, a temporary endocardial pacing catheter, or an alternative induction method at the discretion of the investigator. If conversion testing is performed during the initial implant procedure (or at any subsequent follow-up-scheduled or unscheduled) the following definitions will be applied to the testing with respect to data collected on the case report form:

- A *successful conversion* is defined as any shock delivered by the S-ICD pulse generator that terminates the induced VT/VF arrhythmia (device declared end of episode) and does not require an external defibrillator. This includes episodes where VT/VF converts but an atrial tachyarrhythmia may persist.
- A *failed conversion* is defined as the need for an external defibrillator following the inability of the S-ICD pulse generator to convert the VT/VF arrhythmia.
- An *attempt* is defined as an induction resulting in VT/VF that does not receive therapy (most probably due to the rhythm breaking prior to delivery of shock) and/or an induction not resulting in VT/VF.

7.3.3 Initial Device Set-Up and Programming

All device programming is at the discretion of the Investigator.

7.3.4 X-Ray Documentation of System Position

Any X-ray images that are obtained to document the final positioning of the S-ICD pulse generator and subcutaneous electrode will be collected.

7.3.5 Implant Data

Table 5 lists the data that will be requested from the implant procedure if available.

Table 5: Implant Data Collection

Data Collection	Retention of Originals
Medications (antibiotics; type of anesthesia etc.) Clinical events including System related complications, major cardiac procedures, Hospitalizations and deaths Medical notes/worksheets documenting implant time; use of fluoroscopy, VT/VF inductions etc.	Investigational Centre
S-ICD programmer printouts: Initial and Final Summary Reports Captured S-ECG Implanted Product and accessories utilized for S-ICD System (model/serial/lot/batch/etc.) Chest X-ray(s), if applicable SD Card, if applicable	Investigational Centre and e-Copy to Boston Scientific, if requested Boston Scientific (e.g. via CAMELION)

7.4 Scheduled Follow-ups up to 360 Days Post Implant

All scheduled device check follow-ups for at least 360 days post implantation date should be recorded. It is generally not necessary to separately report pre-discharge visits and wound checks unless any of the following have occurred:

- Spontaneous episodes that have not been previously reported
- Programming changes have been made to the implanted S-ICD System (e.g. reprogramming, performing auto set-up, template formation, vector/gain settings, etc.)
- Clinical events

If a patient's follow-up schedule doesn't include an exact 360 day ("12 month") post implant visit, the nearest equivalent should be used such that each patient has *at least* 360 days of data.

7.4.1 Device Programming and Data Collection

All programming is at the discretion of the Investigator. Table 6 lists all the data that will be requested from scheduled follow-ups if available.

Table 6: Follow-Up Data Collection

Data Collection	Retention of Originals
Cardiac Medications Clinical events including System related complications, major cardiac procedures, Hospitalizations and deaths	Investigational Centre
S-ICD printouts: Initial and Final Summary Reports Captured S-ECG Spontaneous Episodes ± therapy Chest X-ray(s) if applicable SD Card if applicable	Investigational Centre and e-Copy to Boston Scientific, if associated with endpoint data Boston Scientific (e.g. via CAMELION)

7.5 Annual Follow-Ups

After all scheduled and unscheduled follow-ups have been collected for the first 360 days of the Registry, data will continue to be collected once annually until either 60

months of patient data have been collected; the patient withdraws from the Registry (or is withdrawn including for reasons of death) or is Lost to Follow-Up.

To aid with centre planning, this annual follow-up should be timed to occur 24, 36, 48 months +/- 90 days and 60 month +90 days post implantation date. Once a patient has a follow-up time of at least 1800 days post implant date they will have completed the study.
All the system-related events and hospitalizations that occurred during the period prior to the annual data follow up, will be collected.

7.5.1 Device Programming and Data Collection

All programming is at the discretion of the Investigator. Table 7 lists all the data that will be requested from annual follow-ups if available.

Table 7: Annual Follow-Up Data Collection

Data Collection	Retention of Originals
S-ICD printout: Initial and Final Summary Report Clinical events including System related complications, Major cardiac procedures, Hospitalizations and deaths Spontaneous Episodes ± therapy Current status of S-ICD system	Investigational Centre and e-Copy to Boston Scientific, if associated with endpoint data

7.6 Unscheduled Follow-up Visits

During the initial 360 day post implant period of data collection, physician office visits, emergency room visits, outpatient hospital visits, and hospitalizations related to the S-ICD System that occur in between scheduled, standard of care follow-up visits should be recorded as an unscheduled follow-up visit. Routine medical visits, unrelated to the S-ICD System do not need to be reported as additional follow-up visits.

If available, the following data should be collected from unscheduled follow-up visits:

- Clinical Events including details of any hospitalizations
- Device Evaluation including printouts of spontaneous episodes
- Chest X-rays

7.7 System Revisions

In the event that any component of the S-ICD System is surgically revised after the initial implant procedure, an additional implant form can be used to record changes to the system. Devices that are explanted, implanted or any additional conversion testing performed can be reported.

7.8 Quality of Life Assessments

Prospective patients enrolled in the Registry, aged ≥18yrs of age and with sufficient understanding of the local language to effectively complete the set of questions, will be given the option to provide assessments of their QOL by completing the following short set of standardized and validated questionnaires:

- Short Form Health Survey (SF 12)
- Florida Patient Acceptance Survey (FPAS)
- Patient ICD Concerns Questionnaire (ICDC)
- Hospital Anxiety and Depression Scale (HADS)
- Type D Scale (DS14)
- EQ-5D

The questionnaires will be given to the patients in local language at baseline and approximately 3 months, 6 months and 12 months post-implant. Patients without a scheduled follow-up falling within these windows will have the questionnaires mailed to them in a pre-paid envelope. A reminder system will be implemented to follow-up on the status of mailed questionnaires. Prior to the mailing of follow-up questionnaires, the survival status of the patient should be checked.

QOL questionnaires will be returned to and analysed by:

Susanne S. Pedersen PhD
Professor of Cardiac Psychology
University of Southern Denmark
Institute of psychology
Campusvej 55
5230 Odense M
Denmark
sspedersen@health.sdu.dk

7.9 Implant and Follow-Up Experience Questionnaires

A survey will be used to document the experiences of the personnel implanting and performing the follow-ups of S-ICD patients at the participating centres. Implant experience questionnaires should be completed by the implanting physicians at each centre at two time points: 1) first prospective enrolment/implant and 2) end of Registry.

Follow-Up questionnaires should also be completed at two time points by personnel responsible for patient follow-up: 1) time of the first scheduled follow-up of the first prospective patient and 2) end of Registry.

8.0 Patient Management

There are no additional follow-up requirements once a patient has been withdrawn from the Registry. The appropriate case report forms can be completed to document withdrawal of any patient from the Registry.

Patients may be withdrawn from the Registry subsequent to enrolment for a variety of reasons including:

- Investigator decision to remove patient from Registry;
- Patient is lost to follow-up despite best effort to locate patient;
- Patient declines further participation in the Registry after being informed of the risks associated with the system under investigation.

8.1 Withdrawal Requirements

There are no follow-up requirements for enrolled patients that are withdrawn from this Registry prior to the commencement of an implant procedure. Patients that commence, but do not complete an implant procedure should be monitored for any clinical events before being withdrawn from the Registry. Best efforts to monitor any ongoing clinical events to resolution should be made prior to withdrawing a patient from the Registry.

Patients, who had a S-ICD pulse generator or electrode replacement shall continue to be followed within the Registry. Patients, who had a full or partial S-ICD System explant (e.g. due to infection, skin erosion or indication change) shall be followed until all clinical events associated with the explant are resolved.

Specific withdrawal requirements for Sub-Study patients are listed in Appendix E.

9.0 Potential Risks and Benefits

9.1 Analysis of Risks

A complete list of anticipated cautions, warnings and potential clinical events is included in the User's Manual. The risks associated with the use of the S-ICD System are comparable to those associated with the use of any other currently available single or dual chamber ICD; however, the S-ICD System is completely subcutaneous, and therefore, risks associated with the placement of transvenous leads are not applicable.

There are no additional risks for the patients, who are participating in the Sub-Study (see Appendix E) compared to the main study.

Risks associated with the S-ICD System and implant procedure may include, but are not limited to the following:

- 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

9.2 Risk Minimization

Risks associated with the S-ICD System can be minimized by following the detailed instructions in the User's Manual.

9.3 Potential Benefits

This clinical evaluation is intended to evaluate long term clinical outcome associated with the S-ICD system. Specific benefits have not been proven; however, the S-ICD System does not require any component of the system to be placed in the vasculature or the heart, and therefore, eliminates risks and complications associated with transvenous lead placement.

The patient may not receive any benefit from participating in this study. However, results from the data collected during this study may improve the management of S-ICD patients in the future.

10.0 Clinical Events

10.1 Clinical Event Definitions

Adverse Event – Any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the system under investigation.

Adverse Device Effect- Any untoward or unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or deployment of the device. It also includes any event that is a result of user error.

Serious Adverse Event – A clinical event that:

- Led to a death;
- Led to a serious deterioration in the health of the subject that:
  - resulted in a life-threatening illness or injury,
  - resulted in a permanent impairment of a body structure or a body function,
  - required in-patient hospitalization or prolongation of existing hospitalization,
  - resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect- An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune

Observation – A clinical event that does not result in invasive intervention. Examples of such non-invasive intervention include, system reprogramming, antibiotic treatment of pocket infection, or change in medications.

Complication – A clinical event that results in invasive intervention. Examples of such invasive intervention include surgical intervention, system repositioning, and system explant.

10.2 Classification of Clinical Events

All clinical events will be categorized as observations or complications. In addition, clinical events will be classified by type as shown below.

Type I:	Caused by the S-ICD System
Type II:	Caused by the S-ICD System User's Manual or labelling of the S-ICD System
Type III:	Not caused by the S-ICD System, but would not have occurred in the absence of the implanted S-ICD System.
Type IV:	Caused by a change in the patient's condition
Type V:	Not a clinical event (not an observation or a complication)

10.3 Steering Committee

A Steering Committee will be created to evaluate and drive publications as well as to oversee other tasks associated with the conduct and outcome of the Registry.

10.4 Patient Death

Investigators should report any patient death to the Registry sponsor as soon as possible. If possible, the S-ICD System should be removed from the patient, and returned to Boston Scientific for analysis and the data related to the death recorded as appropriate in the database. If possible, a detailed death letter should also be provided to the Registry sponsor.

In the event that the S-ICD pulse generator or subcutaneous electrode cannot be removed, the S-ICD pulse generator should be interrogated prior to interment if possible. Remove the S-ICD from a deceased patient prior to cremation. The device battery may explode when exposed to extreme temperatures.

All patient deaths experienced during the Registry will be reported by the Registry sponsor to the appropriate regulatory agencies in line with individual countries' vigilance reporting requirements.

10.5 Clinical Event Reporting

10.5.1 Investigator Responsibilities

Per ISO 14155:2009, the Investigator should report all clinical events to the Sponsor in a timely manner.

10.5.2 Sponsor Responsibilities

Boston Scientific will report all clinical events reported by investigators per applicable geographies' requirements. The Sponsor will inform all Principal Investigators in writing of all reported serious adverse events and serious adverse device effects that have been reported.

11.0 Responsibilities

11.1 Sponsor Responsibilities and Contact Information

The Sponsor or Sponsor's representative is responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring appropriate monitoring of the investigation, ensuring that EC review and approval are obtained as required and ensuring that any reviewing EC or applicable Regulatory Agency is promptly informed of significant new information about an investigation.

Questions regarding this Registry should be directed to the local Boston Scientific representative or designee. Alternatively, questions or reports of serious adverse events or serious adverse device effects may be directed to:

Jana Meschede
Clinical Trial Manager
Boston Scientific
Lambroekstraat 5D
1831 Diegem, Belgium
Tel : +49 160 90 160 846
Jana.Meschede@bsci.com

11.1.1 Role of Boston Scientific Personnel

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 Boston Scientific equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, Boston Scientific 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
- Performing electrode diagnostic testing
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from programmers and other equipment
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff.

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

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

Boston Scientific personnel will not do the following.

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

11.2 Investigator Responsibilities

Investigators are responsible for the following:

- Ensuring that the Registry is conducted according to any signed agreements, the Protocol and applicable regulations for protecting the rights, safety, and welfare of subjects under the investigator's care
- Ensuring that the Registry is conducted with the express approval of the Institution's EC or providing appropriate documentation that such approval is not required per Local/National regulations
- Ensuring that conducting the Registry will not give rise to conflicts of interest
- Informing the Sponsor in writing of the reason(s) for any withdrawal of any EC approval
- Ceasing the enrolment of patients immediately in the event of the withdrawal of any EC approval
- Ensuring that no patients will be enrolled, without prior, written Approval to Enrol from the Sponsor
- Agreeing to use their best efforts to satisfactorily complete the planned work and to comply at all times with accepted good clinical practice.
- Informing the sponsor of any conditions under which prior research was terminated
- Ensuring that informed consent is obtained appropriately and that the conditions of informed consent are complied with
- Ensuring the appropriate completion of all case report forms with the understanding that certain records and reports may be submitted to regulatory agencies by the Sponsor to support regulatory submissions
- Maintaining all records as described in the Protocol
- Supporting a monitor/auditor (as applicable) in their activities

- Informing the Sponsor of all adverse events and adverse device effects in a timely manner and informing the EC of any serious adverse device effects as applicable
- Providing electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations.

11.3 Enrolment Commencement Requirements

Investigators will be required to submit the following documents to the Sponsor prior to the first patient enrolment:

- Current curriculum vitae of investigator and co-investigators;
- Signed Protocol Signature Page (all centres)
- Signed Clinical Trial Agreement or equivalent;
- Signed Financial Agreement (separate or incorporated with a clinical trial agreement)
- Documentation that the study has obtained appropriate EC approval acceptable to the Investigators' institution or that such approval is not required per local/national guidelines
- Approved Patient Consent Form;

The principal investigator at each investigational centre is responsible for the proper conduct of the trial at the centre. Some responsibilities may be assigned to co-investigators or other appropriately trained personnel, at the clinical centre; however, the principal investigator remains responsible for the proper conduct of the clinical investigation.

12.0 Compliance

12.1 Monitoring

This investigation will be monitored in accordance with the monitoring plan by personnel from the Sponsor or working on behalf the Sponsor.

12.2 Controlling of Devices

12.2.1 Device Distribution

The S-ICD system will be available for distribution at all centres involved in the clinical investigation, therefore devices will be distributed and tracked per standard processes associated with commercial product.

12.2.2 Return of S-ICD Systems

In the event that any product needs to be returned due for example to explant or perceived malfunction, the contact information for Boston Scientific Customer Service is as follows:

Technical Services Contact:

BSC CRM Technical Services Staff / USA
Toll-Free Phone: 1-800-CARDIAC (1-800-227-3422)

BSC CRM Technical Services staff/ International

Technical Service Department

Global Therapy System Support

Green Square, Lambroekstraat 5D

1831 Diegem, Belgium

Tel: +32(0)2 416 72 22

Fax: +32(0)2 416 72 12

eurtechservice@bsci.com

12.3 Informed Consent

Unless otherwise dictated by local or National guidelines governing the study, written informed consent is required from all patients or their legal representative, prior to participation in this Registry. The Sponsor/ or Sponsor's representative will provide a template informed consent document in local language. For centres where EC approval is required, the informed consent should also be approved. In the event no EC approval is required, the final version of the informed consent will be agreed between the Sponsor/ or Sponsor's representative and the investigational centre. Significant changes to the consent document provided by the Sponsor may need to be reviewed and approved by Boston Scientific before a patient provides written informed consent.

If new information becomes available that can significantly affect a patient's future health and medical care, that information shall be provided to the patient(s) affected in written form. If relevant, all affected patients shall be asked to confirm their continuing informed consent in writing.

12.4 Securing Compliance

Boston Scientific or its representative is responsible for ensuring investigator compliance with the clinical protocol, the investigator agreement and applicable regulatory requirements. Boston Scientific will attempt to secure compliance by discussing non-compliances and corrective actions with investigators in person, on the telephone, or in writing. Boston Scientific reserves the right to terminate investigators' participation for continued non-compliance.

12.5 Patient Confidentiality

Patient data will be treated as confidential information by Boston Scientific. Boston Scientific will limit access to confidential information to those individuals requiring access. Regulatory agencies maintain the right to review records pertinent to this clinical study. Unless required by law, Boston Scientific will report de-identified data in an effort to secure patient confidentiality.

13.0 Records and Reporting

Records must be maintained by Boston Scientific or its representative and all Investigators in accordance with local and national regulations and ISO 14155:2009.

Original source documentation must be maintained at the investigational centre to substantiate data entered on case report forms.

13.1 Investigator Records

Investigators are required to maintain complete and accurate records pertaining to the study. Relevant records include:

- EC approvals, renewals, and withdrawals;
- Records of systems used in the study, including traceability to the patient that received the system;
- Records of any systems returned to Boston Scientific;
- Signed informed consent forms for each enrolled patient;
- Completed case report forms;
- Records of all clinical events and supporting documentation;
- Records pertaining to the death of any patient participating in the study;
- Copies of the current approved version of the protocol.

Records should be maintained for at least 2 years following the completion or termination of the investigation or the time dictated by National guidelines if longer.

13.2 Protocol Deviations

This is an observational, standard of care, clinical evaluation. Deviations will only be issued for the following events:

- Inappropriate or unavailable informed consent
- Inclusion/exclusion criteria violations

13.3 Investigation Centre & EC Information

As the study sponsor, Boston Scientific and/or it's representative, will maintain a record of all participating centres, their Principal and Co-investigators and details relating to their reviewing ECs. This information will be provided by the study Sponsor upon request.

13.4 Amendments to the Protocol

In the event an amendment to the protocol is required, the study Sponsor or Sponsor's representative will inform all Principal Investigators in writing including an explanation of any reason for change. Patients may not be enrolled according to the requirements of any amendment until appropriate approval is obtained including the EC approval as required

13.5 Premature Termination

Should the EFFORTLESS S-ICD Registry be terminated prematurely for any reason, all Principal investigators will be notified in writing including the reason for termination.

Appendix A S-ICD Principle of Operation

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

Pulse Generator

The S-ICD pulse generator comprises an inner structure of discrete electrical components, interconnected low power and high power hybrid assemblies, batteries, and high energy capacitors. The inner assembly is enclosed in a hermetically sealed can with a pre-molded polyurethane header for electrode connection. The header contains a single port for connection of the subcutaneous electrode to accommodate sensing, pacing, and defibrillation.
The pulse generator is designed to provide defibrillation therapy using a constant tilt biphasic waveform. The pulse generator is capable of delivering high energy defibrillation shocks as well as bradycardia demand mode cardiac pacing for a period up to thirty seconds following defibrillation therapy.

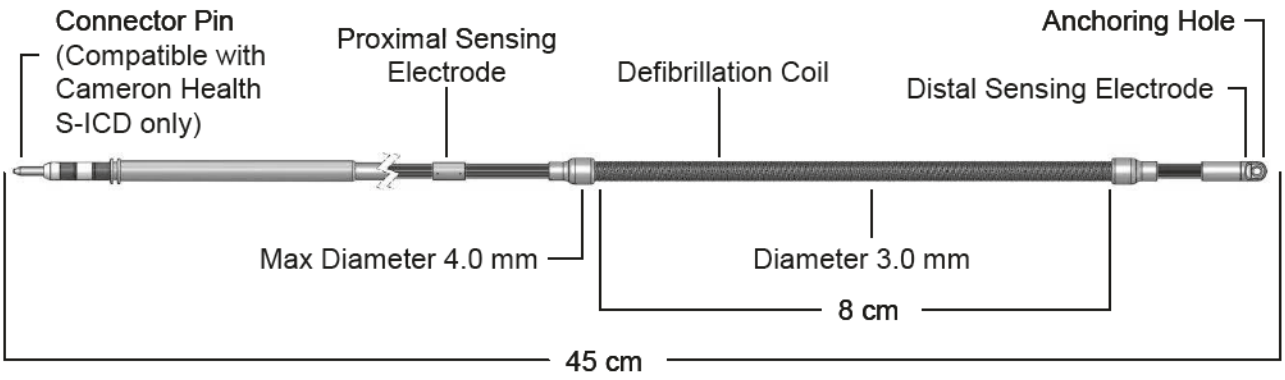
The first generation of the S-ICD pulse generator is called SQ-RX. The second generation pulse generators are the EMBLEM and EMBLEM MRI S-ICDs, which are MR Conditional.

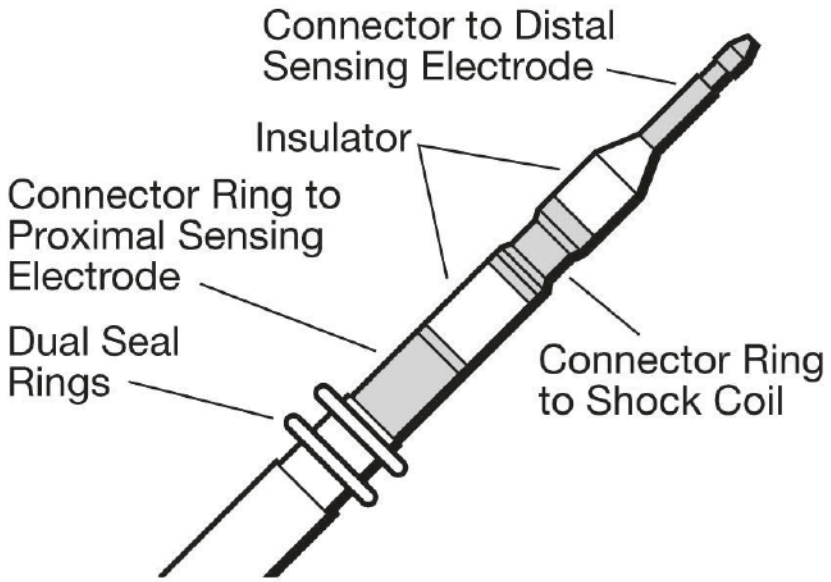
Subcutaneous Electrode

The subcutaneous electrode comprises one high voltage defibrillation coil for the purpose of providing defibrillation energy. It is constructed using multifilars of metallic wire formed into a coil. The subcutaneous electrode is also equipped with a proximal and distal sense electrode, which enables the S-ICD System to evaluate multiple sensing vectors in order to identify the best sensing vector to use for each patient. The sense electrodes are constructed using metallic tubing mechanically affixed to the body of the electrode. 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 electrode and is subcutaneously implanted from the device pocket along the rib margin to the sternum. The proximal termination of the subcutaneous electrode comprises a multi-pole connector to plug into the header of the pulse generator. This connector is designed to be compatible with the Boston Scientific S-ICD pulse generator only.

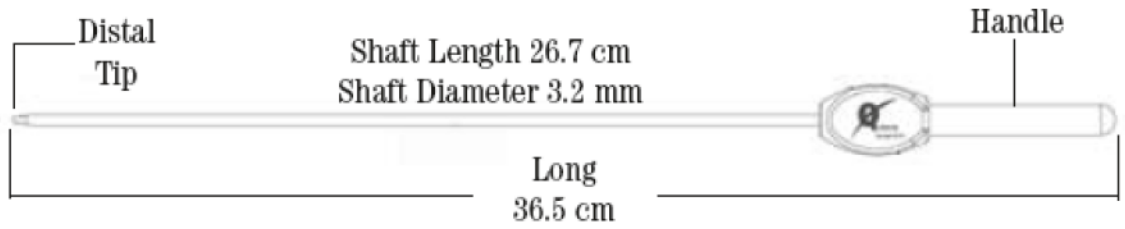
Q-TRAK was the first generation subcutaneous electrode for the S-ICD System. The new electrode is called EMBLEM.





Electrode Insertion Tool

The Electrode Insertion Tool (EIT) is a single use, disposable subcutaneous tunnelling tool which 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 electrode through a subcutaneous sinus.



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 and/or keyboard. The unit operates off of a rechargeable lithium ion battery pack or AC power via its wall power source.

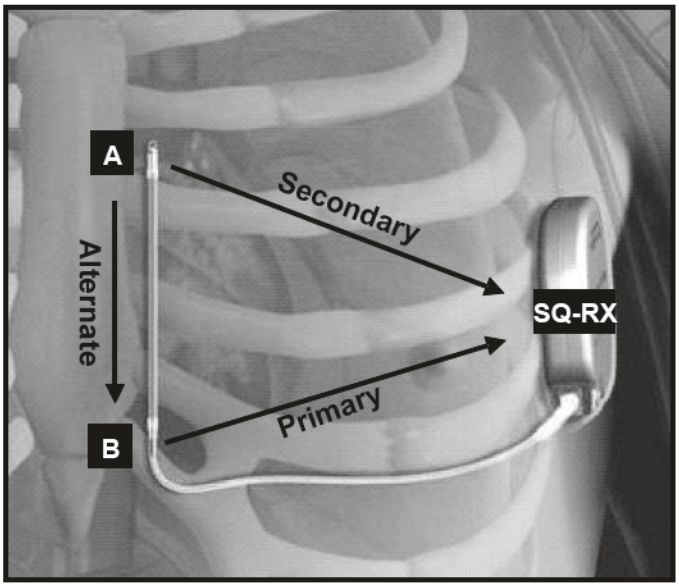
Communication between the pulse generator and the programmer is accomplished through an RF telemetry wand. The radio link operates in the Medical Implant Communication Service band specified in EN 301 839-1:2002 and complies with applicable FCC regulations. The programmer is capable of recognizing multiple 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. S-ICD programmer functionality includes:

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

S-ICD System Sensing and Detection

Prior to the commencement of sensing and detection of normal sinus rhythm (NSR) and/or arrhythmic events, Sensing Setup must be performed. This setup procedure may begin once the S-ICD pulse generator and subcutaneous electrode are implanted and connected.



The S-ICD System incorporates three possible sensing vectors: (1) Primary; (2) Secondary; and (3) Alternate. A Vector Selection algorithm is designed to automatically select the best sensing vector from the available vector choices. The algorithm measures critical components of the S-ECG signal and determines the best vector through analysis of signals recorded through these components. A Sense Vector Optimization algorithm is designed to incorporate the effect of posture into the vector selection algorithm.
The optimization is skipped during the implant procedure when positioning the patient in multiple postures in not practical. However, when utilized post-implant, the optimization algorithm will evaluate changes in sensing qualities that result from patient posture changes. A Reference ECG Acquisition (Template Formation) algorithm is designed to store the morphology of the patient's ECG during normal sinus rhythm. This template is later used while the S-ICD System continuously monitors the subcutaneous ECG for any tachyarrhythmia events.

Defibrillation Therapy

Once a defibrillation shock is deemed necessary, the pulse generator charges and up to 5 maximum energy (80 J) shocks are delivered for each episode. The defibrillation waveform is a truncated exponential, 50% tilt, biphasic waveform delivered between the pulse generator and the subcutaneous electrode coil. With the exception of shocks delivered manually or during induction testing, shock energy level is non-programmable and set to the maximum (80 J) output. The S-ICD System attempts to deliver all shocks synchronously with a detected cardiac event. An Adaptive Shock Polarity algorithm is designed to automatically select the polarity for the first shock delivered, based on the polarity of the last delivered successful shock. The algorithm will automatically alternate shock polarity for any necessary subsequent shocks.

Post-Shock Pacing

When programmed ON, the S-ICD System will deliver post-shock bradycardia pacing at a rate of 50 ppm for a maximum duration of 30 seconds. At the onset of post-shock sensing, a post-shock pacing escape interval is initiated. If one or more detections occur during this escape interval, post-shock pacing is deactivated. Once post-shock pacing is initiated, pacing is delivered in a demand mode and pacing will stop if an intrinsic rhythm is detected. The post-shock pacing waveform is a constant current, 200 mA, biphasic pulse with a pulse width of 7.5 ms per phase.

Induction of Arrhythmias for Device Testing

The pulse generator delivers an induction waveform when commanded by the S-ICD programmer. The 200 mA, 50 Hz AC induction waveform is delivered between the pulse generator and the subcutaneous electrode coil. The induction waveform is delivered until the induction button on the programmer is released. The programmer limits the induction waveform to a duration of 10 seconds. A subsequent induction waveform can be delivered by releasing the induction button and reselecting it once available.

Episode History

The pulse generator stores treated and non-sustained spontaneous episodes for subsequent retrieval using the programmer. The programmer displays the number of episodes, both spontaneous treated and non-sustained, as well as the number of delivered therapy shocks since the last follow-up. This data is automatically cleared when the programmer session is ended. An Episode Begin is declared at the onset of capacitor charging. Arrhythmias that terminate prior to the onset of capacitor charging are not retained. An Episode End is declared when the Tachycardia to NSR transition occurs following 24 intervals below the lowest programmer therapy zone.

An episode is considered treated when at least one shock has been delivered. Episodes are stored in a first-in-first-out format; however, the first stored treated episode is never overwritten.
An episode is considered non-sustained if capacitor charging occurs without the need to deliver any shocks. Non-sustained episodes are stored in a first-in-first-out format. All non-sustained spontaneous episodes have equal priority.

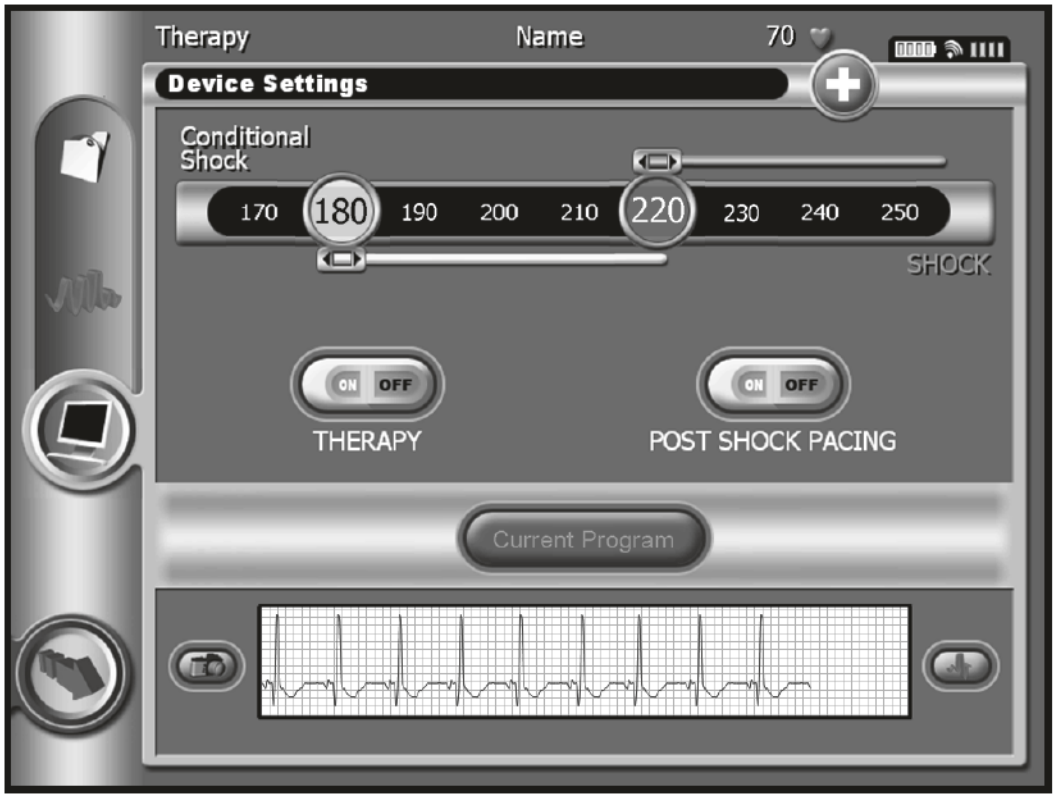
The EMBLEM MRI S-ICD stores additionally one atrial fibrillation (AF) episode for each day in which atrial fibrillation is detected. Up to seven of the most recent AF episodes can be stored.

Programmable Parameters

The following programmable parameters are available from the Main Programming Screen of the programmer.

- *Therapy ON/OFF* - Automatic Therapy is programmable with the Therapy ON/OFF switch. Therapy ON allows the pulse generator to invoke the detection algorithm and automatically treat ventricular arrhythmias. When Therapy is programmed OFF, manual shocks (including Rescue Shock) remain available. When the pulse generator is first taken out of Shelf mode, Therapy OFF is programmed.
- *Post-Shock Pacing ON/OFF* – Post-Shock Pacing is programmable with the Post-Shock Pacing ON/OFF switch. When programmed ON, the pulse generator automatically delivers Post-Shock Pacing as required following shock delivery. When programmed OFF, the pulse generator will not deliver Post-Shock Pacing for any delivered shocks.
- Therapy Zones - Two therapy zones are available for programming: Shock Zone and Conditional Shock Zone (optional). Nominal settings are configured with the Shock Zone at 200 bpm and the Conditional Shock Zone OFF.

- *Shock Zone* – Programmable from 170 – 250 bpm in increments of 10 bpm.
- *Conditional Shock Zone* – Programmable as OFF or from 170 – 240 bpm. If the Conditional Shock Zone is not OFF, it must be at least 10 bpm below the Shock Zone.



For the latest S-ICD pulse generators, the following parameter can be programmed from the SMART settings screen:

- *SMART Pass ON/OFF*– The SMART Pass feature activates an additional high-pass filter designed to reduce oversensing and the number of inappropriate therapies while maintaining an appropriate sensing margin. The device continuously monitors the ECG signal amplitude and disables SMART Pass if under-sensing is suspected.

For future generations of the Boston Scientific S-ICD System, please refer to the User's Manuals for any updates in the principle of operation.

Appendix B Acronyms and Definitions

AF	Atrial Fibrillation
bpm	Beats per minute
CEC	Clinical Events Committee
cm	Centimetre
CRF	Case Report Form
DFT	Defibrillation Threshold Test
EC	Ethics Committee
ECG	Electrocardiogram
EIT	Electrode Insertion Tool
GCP	Good Clinical Practice
GUI	Graphical User Interface
HCP	Health Care Professional
Hz	Hertz
ICD	Implantable Cardioverter Defibrillator
J	Joules
KM	Kaplan Meier
LVEF	Left Ventricular Ejection Fraction
mA	Milliampheres
mm	Millimetre
ms	Millisecond
mV	MilliVolt
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
QOL	Quality of Life
PCMCIA	Personal Computer Memory Card International Association
ppm	Pulses per minute
RF	Radio Frequency
SCD	Sudden Cardiac Death
sec	Seconds
S-ICD	Subcutaneous ICD
SVT	Supra Ventricular Tachycardia
SVGA	Super Video Graphics Array
TV-ICD	Transvenous Implantable Cardioverter Defibrillator
VF	Ventricular Fibrillation
VT	Ventricular Tachyarrhythmia

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Appendix D Investigator Signature Page

Protocol Title:
Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD – The EFFORTLESS S-ICD Registry

Protocol Version:
AB, dated May 04, 2017

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the trial as described in the protocol and in accordance with applicable laws and regulations. In addition, when applicable, I agree to enlist subinvestigators who also agree to perform and conduct the trial as described in the protocol.

PRINCIPAL INVESTIGATOR:

Name: _____

Signature: _____

Date: _____

Appendix E EFFORTLESS S-ICD Extension Phase Sub-Study

In the past the 10-year follow-up has been a key milestone for transvenous ICD systems, as the industry average transvenous ICD longevity is approximately 8 years[34] and transvenous lead failures occur around 8-10 years post implant.[9]

The first generation S-ICD (SQ-RX) has a projected longevity of approximately 5 years. However the EFFORTLESS S-ICD Registry documents operational and clinical outcomes only up to 5 years after the implant. For this reason little data is available on the success of S-ICD System replacements. This includes pulse generator replacements because of elective replacement indicator (ERI) battery status and electrode replacements. In addition some patients require over time a system replacement due to an indication change, as for example a need for pacing.

This Sub-Study will extend the Registry in order to collect long-term follow-up data on a subset of EFFORTLESS S-ICD patients to achieve an average of approximately 8 years of follow-up from index procedure. Approximately 200 patients will be enrolled in the Sub-Study at a sub-set of EFFORTLESS S-ICD sites. The Sub-Study patients will preferably be recruited from the active EFFORTLESS S-ICD patient population. Patients, who have already completed the EFFORTLESS S-ICD Registry in the past, shall be considered secondarily for participation in the Sub-Study. To reduce the selection bias, the patients shall be screened and approached for consent consecutively.

The expected duration of the extension phase is approximately 72 months.

The following data will be analysed in addition of the main study endpoints:

Primary Analysis

- Rate of long-term S-ICD system-related adverse events
- S-ICD replacements for functionality (e.g. pacing, CRT, ATP etc.)
- Device longevity

Secondary Analysis

- Rate of electrode failures and revisions, including the reason for revision
- Rate of device failures and revisions, including the reason for revision
- Rate of complications related to the S-ICD replacements
- Appropriate therapy for VT/VF
- Inappropriate shock therapy (e.g. atrial fibrillation, supraventricular tachycardia)

The following observational data will be collected and analysed additionally to the main study:

- Generator changes/electrode revisions
- VF induction testing at replacement
- Complications associated with S-ICD to TV-ICD change
- Additional invasive interventions (e.g. VT ablation)
- Use of anti-arrhythmic drugs
- Ventricular cycle length of episodes
- Duration (non-sustained episodes)

Patients enrolled in the Sub-Study must meet all inclusion criteria and none of the exclusion criteria as described below.

Inclusion Criteria

1. Subjects who are actively enrolled in the EFFORTLESS S-ICD Registry OR Subjects who completed the 5-year follow-up in the EFFORTLESS S-ICD Registry. All clinical events, spontaneous and induced episode data and system replacement or revision data since the last EFFORTLESS S-ICD Annual Follow-Up of the main study must be available in medical files or equivalent.
2. Subjects who are actively implanted with an S-ICD pulse generator (SQ-RX, EMBLEM or EMBLEM MRI) and an S-ICD electrode (Q-TRAK or EMBLEM) or any other future commercial available versions
3. Willing and able to provide written informed consent or have informed consent as provided by a legal representative and willing to participate in all testing and follow-ups as described the Sub-Study protocol
4. Age 18 or above, and of legal age to give informed consent specific to national laws

Exclusion Criteria

1. Subjects with device replacement from the S-ICD to a transvenous ICD
2. Subjects with unipolar pacemakers or implanted devices that revert to unipolar pacing
3. Subjects that are participating in any other investigational study that may interfere with interpretation of the Registry results, without the written approval of Boston Scientific

Once a patient is enrolled in the Sub-Study, the visit schedule according to Table 8 must be followed. Patients, who have still been actively enrolled in the main EFFORTLESS S-ICD Registry will be waived from the visit requirements as described in Table 3 (Section 7.1) and will be followed-up according to Table 8 only.

Table 8: Summary of information requested for the Sub-Study

	Sub-Study Enrolment Visit	Sub-Study Annual Follow-up Visit	S-ICD System Replacement or Revision
Sub-Study Informed Consent	X	--	--
Demographics	X	--	--
Antiarrhythmic Medication	X	X	X
Episodes (Spontaneous or Induced)	X	X	X[A]
Final Summary Report	X	X	X[A]
Surgical documentation	--	--	X
VT/VF Defibrillation Testing	X[A]	--	X[A]
Adverse Events	X	X	X

[A] If done/If available

Sub-Study Enrolment Visit

The patients shall be enrolled in the Sub-Study at the earliest convenience. A patient is considered enrolled for the Sub-Study after providing written informed consent in accordance with applicable local and national guidelines and/or Ethics Committee (EC) requirements. Sites will be notified when enrolment in the Sub-Study is complete.

The informed consent date, patient demographics and the antiarrhythmic drugs will be collected for all enrolled patients. All device related events, including spontaneous or induced episodes and system replacements or revisions, if applicable, and all adverse events, which occurred since the last EFFORTLESS S-ICD Annual Follow-up will be documented retrospectively.

Table 9 lists the data that will be requested at the Enrolment visit. For the data collection requirements of replacements and revisions please refer to Table 11.

Table 9: Sub-Study Enrolment Visit Source Documentation Requirements

Data Collection	Retention of Originals
Sub-Study Patient Consent Form Demographics (Physical) Antiarrhythmic Medications All Adverse Events since last reported EFFORTLESS S-ICD Annual FU	Retain at center
Spontaneous Episodes ± therapy, including Episode reports since last EFFORTLESS S-ICD Annual FU S-ICD Final Summary Report	Retain the original at the center and submit a copy to to Boston Scientific

Sub-Study Annual Follow-Up Visits

The first Annual Follow-up will be done 12 month +/- 90 days after the Sub-Study Enrolment Visit. Afterwards data will continue to be collected once annually. It is recommended that the subsequent Annual Follow-ups occur 24, 36, 48 and 60 months +/- 90 days from the date of the Sub-Study Enrolment Visit.

The subjects participation in the Sub-Study is considered concluded upon completion of the 5th Annual Sub-Study Follow-up, the patient withdraws from the Sub-Study (or is withdrawn including for reasons of death) or is Lost to Follow-Up.

All antiarrhythmic medication changes, the current status of the S-ICD System, all episodes and adverse event that occurred during the period prior to the annual data follow up, will be collected.

All programming is at the discretion of the Investigator. Table 10 lists all the data that will be required from Annual Follow-ups, if available.

Table 10: Sub-Study Annual Follow-Up Source Documentation Requirements

Data Collection	Retention of Originals
Antiarrhythmic medication changes Adverse Events	Retain at center
Episodes ± therapy, including Episode report S-ICD Final Summary Report	Retain the original at the center and submit a copy to Boston Scientific

S-ICD System Replacements and Revisions

In the event that any component of the S-ICD System is surgically revised or replaced (including the replacement with a transvenous ICD) after the initial implant procedure, an additional “S-ICD System Procedure” form must be used to record changes to the system and to document the surgical procedure.

Table 11 lists the data that will be requested in case of a system replacement or revision.

Table 11: System replacement or revision Source Documentation Requirements

Data Collection	Retention of Originals
Reason for replacement or revision Surgical Documentation including: • Medications (antibiotics; type of anesthesia etc.) • Medical notes documenting implant time; use of fluoroscopy etc. • Chest X-rays (posterioranterior & lateral), if applicable • Implanted Product and accessories utilized for S-ICD System (model/serial/lot/batch/etc.) Adverse Events	Retain at center
S-ICD Final Summary Reports of the old and new S-ICD pulse generator, if applicable VT/VF Defibrillation Testing (programmer printout, electrode & shock impedance), if applicable	Retain the original at the center and submit a copy to Boston Scientific

Sub-Study patients, who have an S-ICD pulse generator replacement or device explant (e.g. due to infection, skin erosion or an indication change) shall continue to be followed within the Sub-Study.